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CERVICAL ESOPHAGOGASTRIC ANASTOMOSIS FOLLOWING SUBTOTAL RESECTION OF THE ESOPHAGUS FOR CARCINOMA*

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IN 1942 Churchill and Sweet¹ reported the resection of the lower esophagus and used esophagogastric anastomosis for restoration of the continuity of the alimentary tract. In the same year, Wookey² demonstrated a technic for resection of the cervical esophagus. The entire intervening thoracic esophagus has now been shown to be accessible to treatment by surgical resection and esophagogastric anastomosis.

Garlock and Sweet demonstrated that the principle of esophagogastric anastomosis could be utilized for resection of tumors in the midthoracic esophagus by means of a supra-aortic anastomosis. More recently Garlock and Sweet have described technics for removal of the superior segment of the thoracic esophagus and have employed esophagogastric anastomosis in the cervical region.

Since the technic that we have used for resection of a carcinoma of the junction of the thoracic and cervical esophagus differs somewhat from those previously described, the following case is presented with a follow-up of nine months to demonstrate that this is a worth-while procedure from the point of view of palliation if not a cure.

CASE REPORT

C D (Bellevue Hospital No 1731248), a 68-year-old unmarried magazine salesman, was admitted to Bellevue Hospital on April 6, 1948, with a chief complaint of regurgitating all fluids and food during the three previous days. The patient had had no complaints until two and one-half months before his admission, when he noted that solid food stuck in the upper part of his chest and he began to regurgitate his food two or three minutes after ingestion. There was no nausea and the food returned as taken, mixed with saliva. There was no blood in the regurgitated material. During two months prior to his admission the patient lived on a strictly self-imposed liquid diet. He finally came

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into the hospital when for three days it had been impossible for him to swallow fluids without regurgitation. There had been no pain or cough. There was a 10-pound weight loss. The family history was significant in that a brother and sister had died of cancer. He had smoked six cigars a day for many years and drank moderately but regularly of beer and wine. The only serious illness he suffered in the past was jaundice 30 years previously. There was no history of venereal disease.

Physical examination revealed a thin, elderly man in no acute distress. The neck veins were distended and there was nodular enlargement of both lobes of the thyroid. The trachea was in the midline. There was no lymph-node enlargement. The chest was emphysematous with increased A P diameter. The lungs and heart were not remarkable.

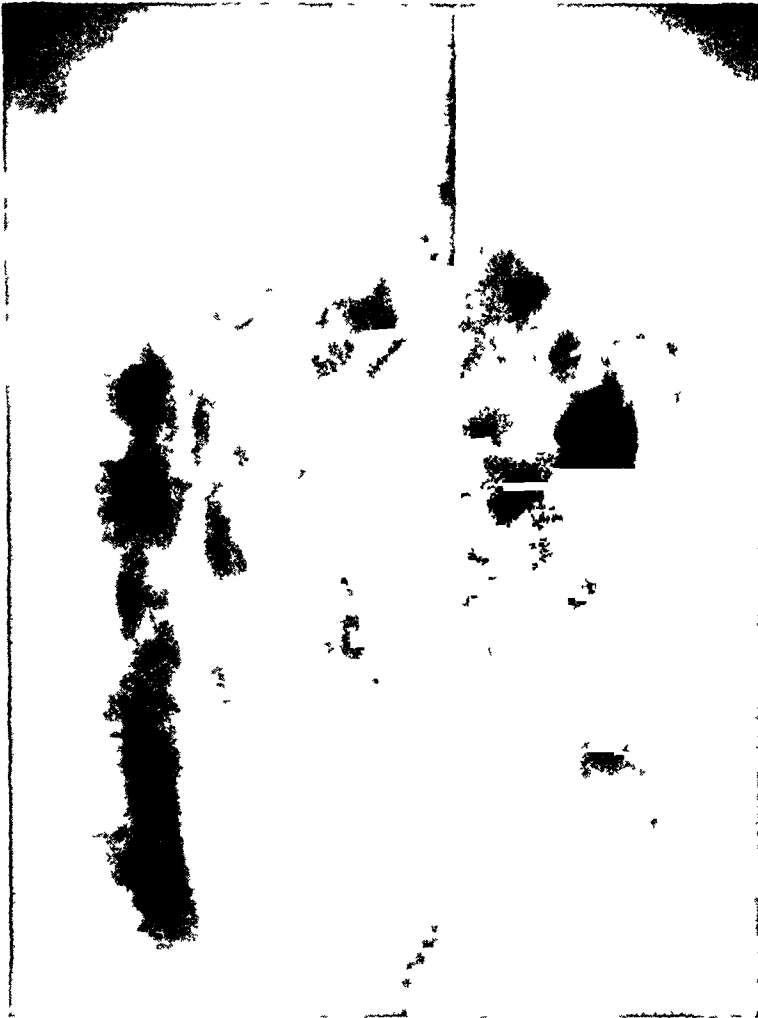


FIG 1—Complete obstruction of the esophagus due to carcinoma in the superior mediastinal segment

The blood pressure was 110/78. The prostate was symmetric but twice the normal size. Fluoroscopic and roentgenologic examination after a swallow of barium showed a complete obstruction of the esophagus at the level of the first rib (Fig 1). Esophagoscopy revealed a stenosing lesion of the upper esophagus, a biopsy of which was reported as a squamous-cell carcinoma. Bronchoscopy was negative.

The day after his admission, the patient was able to take fluids cautiously without regurgitation by the oral route. He was prepared for operation using a high protein

carbohydrate mixture with vitamins Under the regimen he was able to gain back two pounds in the two weeks before operation

Operation On April 26, 1948, the operation was performed under intratracheal cyclopropane anesthesia in the right lateral recumbent position A posterolateral incision was made over the course of the left seventh rib, curving upward at the lateral border of the paraspinal muscles The seventh rib was removed subperiosteally from the cartilage anteriorly, to the transverse process posteriorly A 1-cm portion of the neck of the sixth rib was also excised to facilitate a more adequate opening of the chest The parietal pleura was incised through the bed of the seventh rib and the thorax was widely opened with a rib spreader

After exploration of the mediastinum for metastatic nodes, which were not encountered, an incision was made in the mediastinal pleura along the superior border of the arch of the aorta, curving upward posterior to the subclavian vessels to the dome of the thoracic cavity Here the tumor of the esophagus could be felt as a hard, regular mass approximately 5 cm in length extending upward into the base of the neck At this point resection was decided upon The mediastinal pleura was incised from below the arch of the aorta to the diaphragm The esophagus was mobilized and dissected free from the mediastinum from the diaphragm to the arch of the aorta The vessels from the aorta were secured by ligature and as much of the mediastinal lymphatic tissue as possible was removed with the esophagus The arch of the aorta was mobilized at this point by ligature and division of the upper three intercostal arteries to facilitate the dissection of the esophagus in this region and to allow for future passage of the stomach through this area After dissection of the esophagus from beneath the arch of the aorta, avoiding the recurrent laryngeal nerve, the dissection was then carried above, about the tumor and into the base of the neck At this juncture the thoracic duct was encountered posteriorly in close proximity to the lower border of the tumor It was doubly ligated and divided The dissection was carried out well into the neck above the tumor, first by sharp dissection and then by finger until the operator's finger could be felt in the neck at the level of the cricoid cartilage

With the completion of the dissection of the esophagus within the chest, the diaphragm was widely opened from the esophageal hiatus laterally in the direction of the muscular fibers The phrenic nerve was not disturbed except as its branches were severed in incising the diaphragm The greater curvature of the stomach was freed by incising the gastrosplenic ligament, with ligature and division of the vasa brevia and the left gastro-epiploic vessels as far from the stomach as possible The gastrosplenic omentum was then completely incised to the pylorus, taking care to preserve the right gastro-epiploic vessel on the stomach The stomach at this point was held up to allow dissection and ligation of the left gastric vessels at the coeliac axis The gastrohepatic ligament was incised from diaphragm to pylorus well out from the lesser curvature of the stomach to preserve all anastomotic branches of the left gastric artery In order to mobilize the duodenum more freely, incision of the peritoneum was made along its right lateral border After thus freeing the stomach and duodenum, the stomach could be brought well up into the chest, and the pylorus could be brought up to the diaphragm without tension

A small Payr clamp was placed across the cardiac orifice of the stomach, and the stomach was incised distally Closure of the stomach was then carried out with an over-and-over continuous suture of chromic catgut as the stomach was cut An inverting layer of interrupted 3-0 silk completed the closure of the stomach The distal end of the esophagus was closed by purse-string suture, covered and tied securely within a rubber glove A jejunostomy of the Witzel type was next performed at a distance of about 20 cm from the ligament of Treitz, using a small catheter which was brought out through a stab wound made through the rectus muscle in the left upper quadrant The esophagus was drawn above the arch of the aorta and preparation was made for incision in the neck

The left arm was raised upward and suspended so as to allow access to the left neck Incision was made along the anterior border of the sternocleidomastoid muscle, which

was retracted laterally. The left lobe of the thyroid was enlarged and nodular. A hemithyroidectomy was performed because it was felt that its size would definitely interfere with the intended anastomosis. By incising medial to the carotid sheath and inferiorly, the dissection plane of the esophagus was entered. The esophagus was drawn up into the neck wound and mobilized to the level of the thyroid cartilage. The stomach was then brought up beneath and to the right of the aorta and passed up into the neck through the aperture once occupied by the esophagus. The stomach thus lay in the normal position of the esophagus (Fig 2). The apex of the stomach, which was a point on the greater curvature above the region of the gastrolenal ligament, was fixed by means of interrupted 4-0 silk to the prevertebral fascia of the cervical vertebrae. A row of interrupted mat-

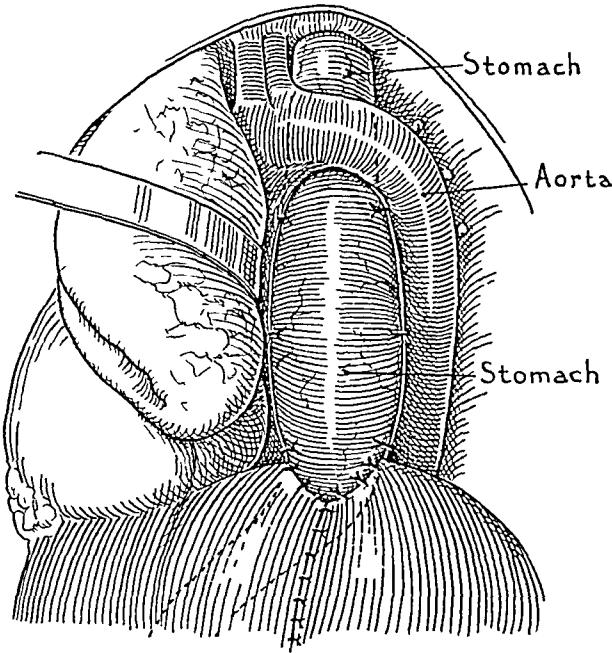


FIG 2—Diagram to show the position of the stomach in the thorax. The aorta has been mobilized by division of the upper three intercostal arteries.

ress sutures was placed between the anterior wall of the stomach and the posterior wall of the esophagus. A vertical incision was made in the stomach, 3 cm in length. The esophagus was cut through, leaving the proximal cut surface for anastomosis. Through-and-through interrupted sutures of 4-0 silk were used to effect an anastomosis, these sutures going through all layers of both organs. Before closure of the anastomosis a Levin tube was passed through and drawn well down into the stomach. A supporting row of interrupted serosal sutures were placed anteriorly. The anterior surface of the stomach below the anastomosis was drawn cephalad and sutured above the anastomosis to the fascia on the thyroid cartilage and the under surface of the sternocleidomastoid muscle. The cervical wound was closed in layers about a small Penrose drain (Fig 3). The stomach within the chest was fixed by interrupted sutures to the aperture at the base of the neck and to contiguous mediastinum down to the diaphragm, which was closed about the prepyloric area with interrupted silk. Through the eighth interspace in the axillary line a large fenestrated tube was introduced into the chest as a drain. The chest was closed in layers with interrupted silk sutures. The operative procedure consumed six and one-half hours, during which the patient received 2,000 cc of blood and

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1,000 cc of 5 per cent glucose in saline for support His condition throughout the procedure was satisfactory

Pathologic examination of the resected esophagus was as follows Macroscopic examination The resected portion of esophagus measures 21 cm in length The proximal portion contains a firm, annular tumor, 4 cm in length, which invades the wall of the esophagus and the adjacent connective tissue The slitlike lumen measures 1 by 5 cm and is not covered with mucosa There is 1 cm of grossly normal mucosa proximal to the lesion, but the tumor appears to extend to the line of surgical excision in the esophageal wall and the adjacent connective tissue

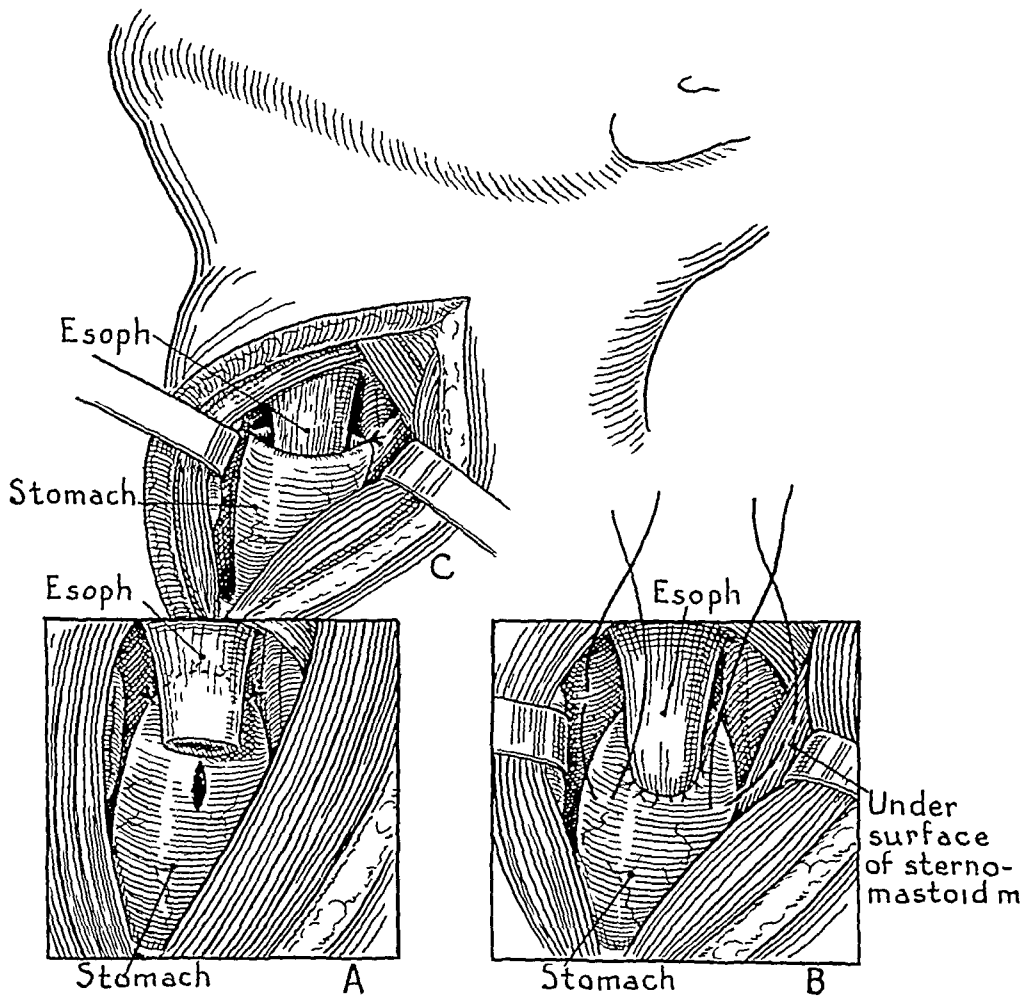


FIG 3—Schematic drawings of an esophagogastric anastomosis in the neck (A) Fixation of the apex of the stomach to the prevertebral fascia and a row of sutures between the posterior wall of the esophagus and the stomach (B) Supporting sutures placed following anastomosis (C) Completed anastomosis

Microscopic examination Sections from the cardia show normal esophagus Sections taken through the anterior wall of the esophagus, containing tumor, show normal stratified squamous epithelium, with the normal underlying wall from the distal portion of the esophagus merging into an area of ulcerated mucosa The underlying wall in this area is invaded by stratified squamous epithelium growing in cords and sheets Pearl formation is frequent The proximal portion of the esophagus is covered with normal-appearing stratified squamous epithelium for a short distance Sections of the thyroid reveal multiple adenomata

Pathologic diagnosis "Squamous-cell carcinoma of esophagus—adenomata of thyroid"

Postoperative Course Between the second and the fourth days postoperatively, the patient had difficulty in raising bronchial secretions and developed several areas of atelectasis in the right lower lung field. This was controlled by means of vigorous and persistent tracheobronchial aspiration. The left lung remained well expanded and the chest tube drain was removed on the fourth day. Feedings were started through the jejunostomy catheter on the second postoperative day, and on the fifth, the nasogastric tube was removed. Fluid was then started cautiously by mouth. On the tenth day the patient was taking a six-feeding diet without difficulty and the jejunostomy tube was removed. At first, only small amounts of food could be eaten because of epigastric pain,



FIG 4

FIG 5

FIG 4—The pylorus is shown immediately below the diaphragm. Note the straightening of the duodenal curve.

FIG 5—A roentgenogram following a swallow of barium shows free flow through the esophagogastric anastomosis in the cervical region.

which ensued if the intake was too large. At the time of his discharge on June 10, 1948, the patient was beginning to gain weight and was eating without any discomfort. His stay in the hospital was prolonged by the complication of urinary retention, due to the benign hypertrophy of the prostate. Roentgen examination two days before discharge revealed evidence of esophagogastric anastomosis with the proximal fourth of the esophagus anastomosed to the stomach. No interference to the passage of barium through the site of anastomosis was noted (Figs 4 and 5).

Follow-Up One month after his discharge from the hospital and two and one-half months after the operation, the patient returned to his work as a magazine salesman, working from 9 to 5 daily except Sundays. When he was last seen, nine months after the operation, he weighed 142 pounds, having gained 36 pounds since his discharge from the hospital. His diet was not restricted and he had returned to his old habit of four glasses of beer a day and most of one bottle of Sherry wine on Saturday night. There has been no regurgitation of food, and the only discomfort he feels is epigastric pain on the rare occasion when he eats too large a meal.

DISCUSSION

In carcinoma of the junction of the supra-aortic thoracic esophagus and the cervical esophagus in which there is no demonstrable evidence of spread of the tumor as evidenced by palpable cervical lymph nodes, involvement of the recurrent laryngeal nerve or encroachment on the trachea by bronchoscopic examination, we believe exploratory thoracotomy is justified to determine operability. Experience may demonstrate, however, that even in those cases that fulfill the above criteria, an initial exploration of the neck may be practical in determining operability.

The decision to use the technic of resection and anastomosis described above was made during the course of the operation, as this method offered the most direct approach to the problem. The mobilization of the stomach through the thorax in the normal position occupied by the esophagus seemed a more direct and natural position for the gastric esophagus than to the left of the aorta, where the route to the neck aperture was more circuitous. The maneuver that was employed in this case of handing up the stomach through the neck by one operator in the chest wound to the other operator in the neck is not entirely satisfactory, but it was felt to be less traumatic to the stomach than using some method of suture to the esophagus for pull through after closure of the chest. It had been planned to remove the medial portion of the clavicle and part of the first rib to give a better exposure for the anastomosis, but in this particular case this procedure did not seem necessary, possibly because the large left lobe of the thyroid had created a greater space than usual in this area of the neck.

The performance of a jejunostomy at the time of operation is probably superfluous when it has been unnecessary as a preoperative means of establishing better nutrition. However, it did provide a good means of keeping up nutrition postoperatively during the six days before it was deemed wise to allow food by mouth.

SUMMARY

A case of carcinoma of the junction of the thoracic and cervical esophagus is presented with resection and esophagogastric anastomosis in the left cervical region. Follow-up of nine months is available on this patient to demonstrate the value of this procedure for palliation, if not for cure.

Note. This patient is alive and well 14 months after operation.

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ONE-STAGE RESECTION OF CARCINOMA OF THE CERVICAL ESOPHAGUS¹ WITH SUBPHARYNGEAL ESOPHAGOGASTROSTOMY

REPORT OF A SUCCESSFUL CASE

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INTRODUCTION

SURGICAL EXTERPATION of carcinoma of the cervical esophagus presents a complex technical problem because of the difficulty in providing a suitable replacement for the resected esophagus when extensive excision is necessary. In 1946, in the course of an operation to remove a supra-aortic carcinoma of the esophagus, the author performed a complete mobilization of the stomach to provide an adequate esophageal substitute. When the esophagogastric anastomosis was made just under the dome of the pleural cavity, an excess of from four to five inches of the gastric tube was available. At that time it was realized that it was technically feasible to bring the stomach into the neck for an esophagogastric anastomosis. Since then, we have explored a small number of cases of carcinoma of the cervical esophagus with the intention of replacing the resected cervical esophagus with the stomach. It was not until September 10, 1948, that an operable case was found. This communication consists of an account of surgical problems encountered in a successful one-stage resection of carcinoma of the cervical esophagus and a subpharyngeal esophagogastrostomy.

Since 1884, various types of skin tubes have been fashioned to replace the resected cervical esophagus.¹⁻⁴ When the tumor extends into the thoracic cavity, it is impossible to employ the simple types of skin tubes. The year 1948 has seen a renewed interest in the treatment of carcinoma of the cervical esophagus. Bricker and Buford⁵ devised a multi-stage method of transplanting a pedicled, skin-lined tube into the thorax to replace the thoracic, as well as the cervical, portion of the resected esophagus. Following the first successful resection of carcinoma of the thoracic esophagus with esophagogastrostomy in this country by Adams and Phemister,⁶ the soundness of the technic of bringing the stomach up into the chest to replace the resected esophagus has been well proved. Sweet⁷ and Garlock⁸ have reported this year the performance of a cervical esophagogastric anastomosis in cases of high intrathoracic carcinoma of the esophagus. Sweet resected the first rib and clavicle with a successful result in two cases. Garlock did not resect the clavicle or rib, but lost his patient on the day after operation. In 1948, O'Donnell,⁹ also, performed a resection of carcinoma of the cervical esophagus with a simultaneous cervical esophagogastrostomy. The cricopharyngeus muscle was severed, with

¹ Submitted for publication, January, 1949.

resultant regurgitation of gastric juice and subsequent pharyngeal ulcers. As far as we know, O'Donnell's and the author's patients represent the only two reported cases of resection of the cervical esophagus, with one-stage esophago-gastrostomy.

CASE HISTORY

W C, a 59-year-old carpenter, was admitted to the hospital on September 6, 1948, complaining of dysphagia of six weeks' duration. Food was regurgitated immediately



FIG 1—Preoperative upper gastro-intestinal series. Irregular obstruction to the flow of barium in the cervical esophagus is seen approximately one and one-half inches above the clavicle. The findings are typical of carcinoma of the cervical esophagus.

after swallowing and he felt an obstruction in his throat. He was able to swallow only liquids, a sip at a time. For 14 months, he had been confined to his home because of a polyarthritis involving the large joints and had lost 50 pounds in weight. There had been an additional weight loss of 15 pounds during the six weeks before his admission. Previously he had been well except that a shell explosion had fractured his right wrist and jaw in World War I.

On examination, a very emaciated, elderly white male was seen who appeared to be chronically ill. The skin was loose and dry. Other positive findings included a barrel-shaped chest with limited expansion. Fine râles were heard at both bases. The heart

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was normal and the abdomen was markedly scaphoid, with the liver edge felt 3 cm below the costal margin. Limitation of motion and swelling of the large joints of the arms and legs were present. No enlarged peripheral nodes were felt.

Roentgen barium study of the esophagus showed an irregular filling defect above the clavicle, typical of carcinoma (Fig 1). On esophagoscopy, a friable tumor was found 2.5 cm below the cricopharyngeus. Biopsy revealed squamous-cell carcinoma, grade III. No gross involvement of the trachea was found on bronchoscopy. Laboratory studies showed hemoglobin, 87 per cent, red blood count, 4,490,000, white blood count, 9,500, polymorphonuclears, 56 per cent, lymphocytes, 36 per cent, mononuclears, 2 per cent, and eosinophiles, 6 per cent. The NPN was 25 mg per cent, serum albumin, 4 per cent, and serum globulin, 2.7 per cent. The urine showed a trace of albumin and rare leukocyte on stained smear. The patient was placed on a 200 Gm protein, high-vitamin,

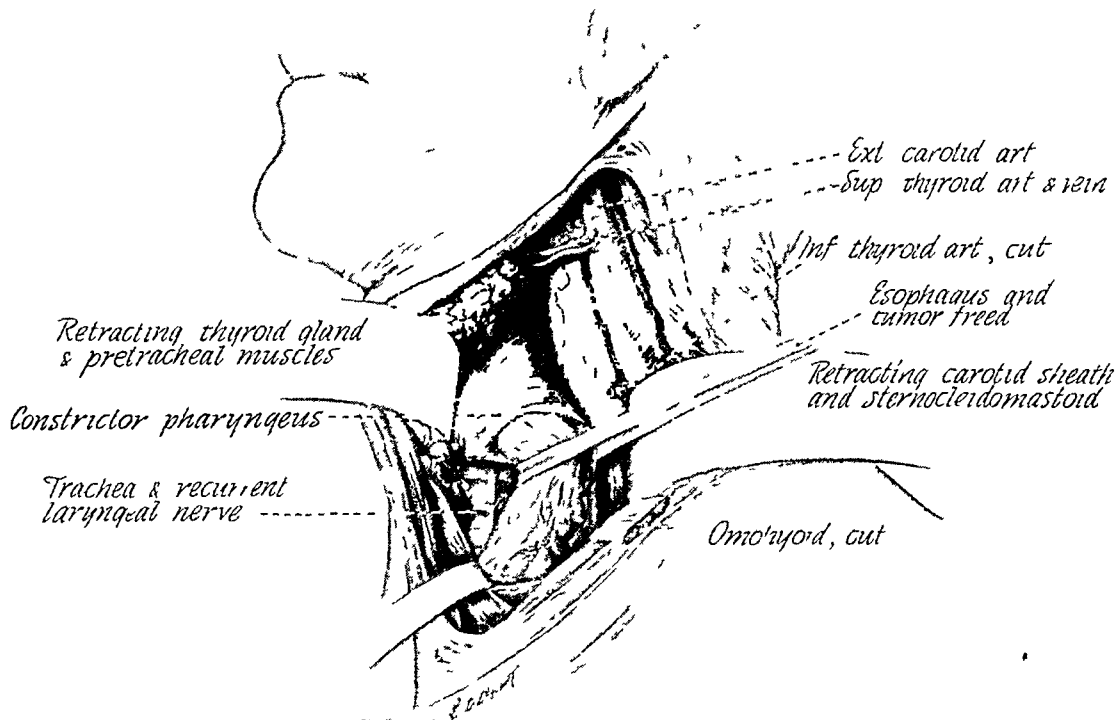


FIG 2—The cervical esophagus has been exposed and freed from the trachea through an incision anterior to the sternocleidomastoid muscle.

3,000-calorie, low-sodium, liquid diet. Three hundred thousand units of penicillin, 1.0 Gm of streptomycin, 1,000 mg of vitamin C, and vitamin B complex were administered intramuscularly daily.

OPERATIVE REPORT

On September 10, 1948, the operation was performed. After a pentothal induction, endotracheal ether-oxygen was used for maintenance. A blood transfusion was started at the beginning of the operation and continued throughout, 2,000 cc being given. The patient was placed on his right side and the left thoracic and cervical regions were prepared for operation. A sterile stockinette covered the left arm, so that it could be moved to give greater exposure of the neck and chest (Fig 3A). An incision was made in the neck, extending from the angle of the jaw on the left down to the suprasternal notch. After severing the platysma, the sternocleidomastoid muscle was retracted laterally. The inferior thyroid vessels were ligated and the carotid sheath retracted laterally. Dissecting behind the thyroid gland, the trachea and the thyroid cartilage were identified.

and the esophagus was found to be infiltrated with a hard, firm mass, obviously carcinoma. By careful dissection, it was possible to free the esophagus from the trachea (Fig 2). Although cancerous tissue was in apposition to the posterior tracheal wall, there was no gross involvement of the trachea. The cancerous tissue extended down into the superior mediastinum. A Penrose sheath drain was placed about the esophagus, which was involved with tumor tissue to approximately 25 cm from the cricothyroid pinch cock.

The chest cavity was opened through an S-shaped incision, centering over the sixth rib (Fig 3A). After severing the muscles of the back, the sixth rib was removed and the fifth and seventh ribs sectioned posteriorly and the seventh anteriorly. An excellent

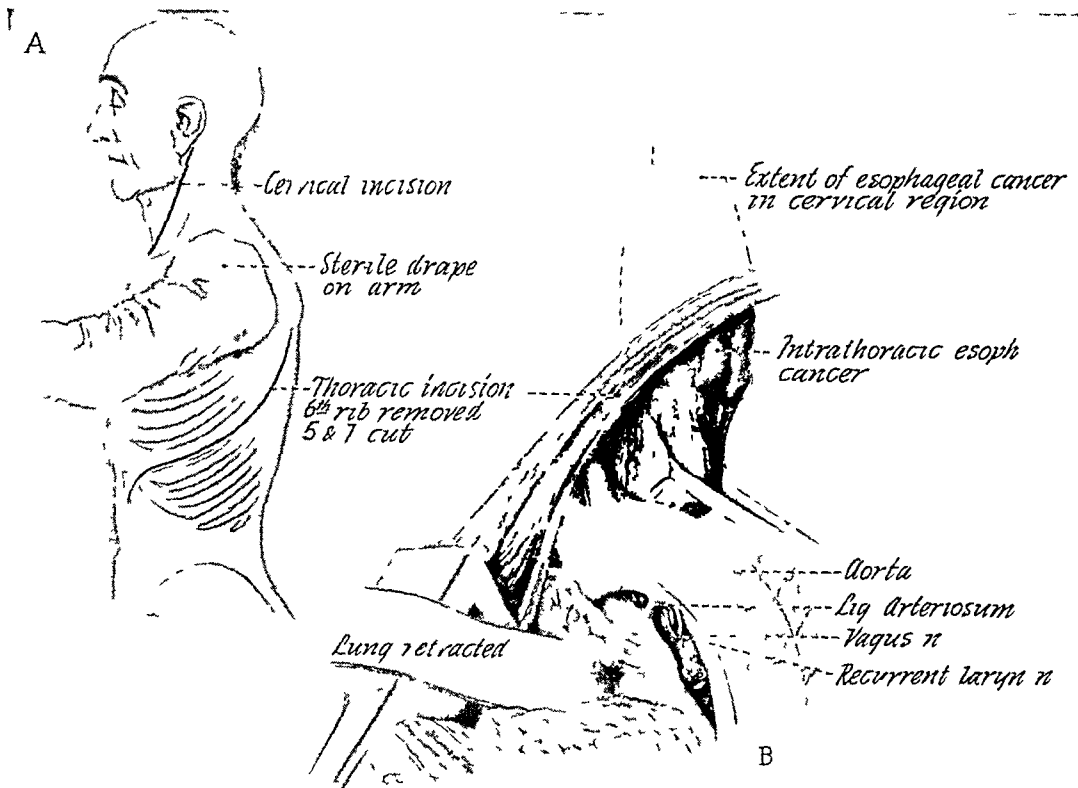


FIG 3—A Cervical and thoracic incisions are used. The patient is lying on his right side. The left arm is covered with a sterile drape. Mobility of the arm facilitates exposure of neck and thorax.

B Freeing of the thoracic esophagus above the aortic arch through the thoracic approach.

view of the entire pleural cavity was obtained. Dissecting into the superior mediastinum, the cancerous tissue seemed to be limited to the esophagus, so that resection was decided upon (Fig 3B).

The diaphragm was incised, starting at the hiatus and extending around to the sternal junction, making a curved incision¹⁰. The stomach was exposed and the mobilization of the stomach was begun by severing the vasa brevia. The left gastroepiploic vessels were saved to preserve the blood supply to the stomach. Reflecting the stomach forward, the coronary vessels were dissected out and ligated, exposing the left gastric artery and vein. The smaller divisions of these vessels were sutured individually to prevent puckering of the lesser curvature of the stomach. Further freeing of the stomach was performed, down to the duodenum, where adhesions binding the pylorus and the first part of the duodenum to the posterior abdominal wall were released to give the

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maximum mobility to the stomach. The thoracic esophagus was exposed by opening the inferior pulmonary ligament, retracting the left lung mesially. The inferior phrenic vessels and the segmental vessels from the aorta were ligated. The esophagus was then mobilized behind the arch of the aorta, taking care not to enter the right pleural cavity. The esophagus was doubly clamped at the cardia with Payr clamps and divided. The cut end of the esophagus was covered with a Penrose drain, which was ligated to prevent leakage of the esophageal contents. The distal end of the esophagus was then turned into the cardia of the stomach and closed with two running layers of No. 0 chromic, reinforced with interrupted sutures of fine silk. The esophagus was then liberated to the point where the cervical esophagus had been mobilized. This was done by ligating the

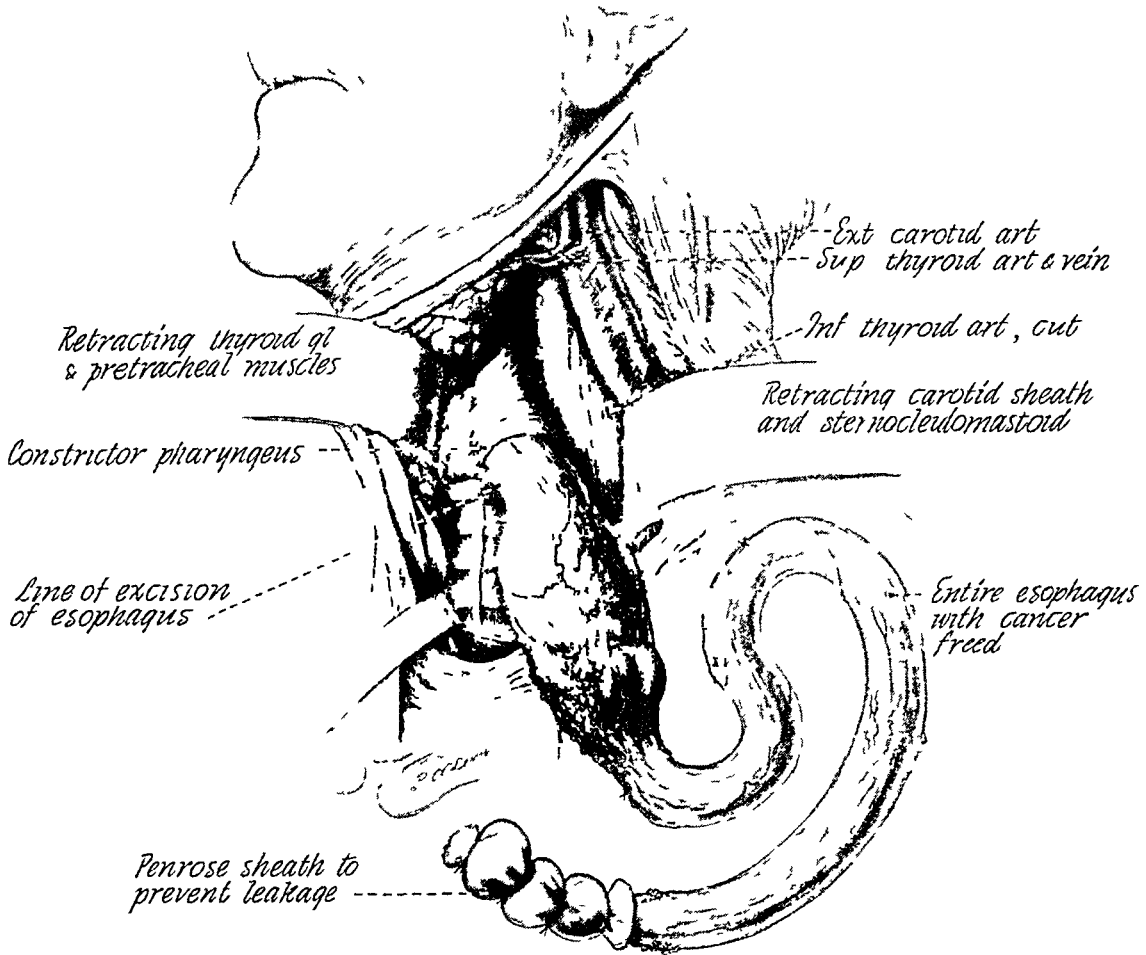
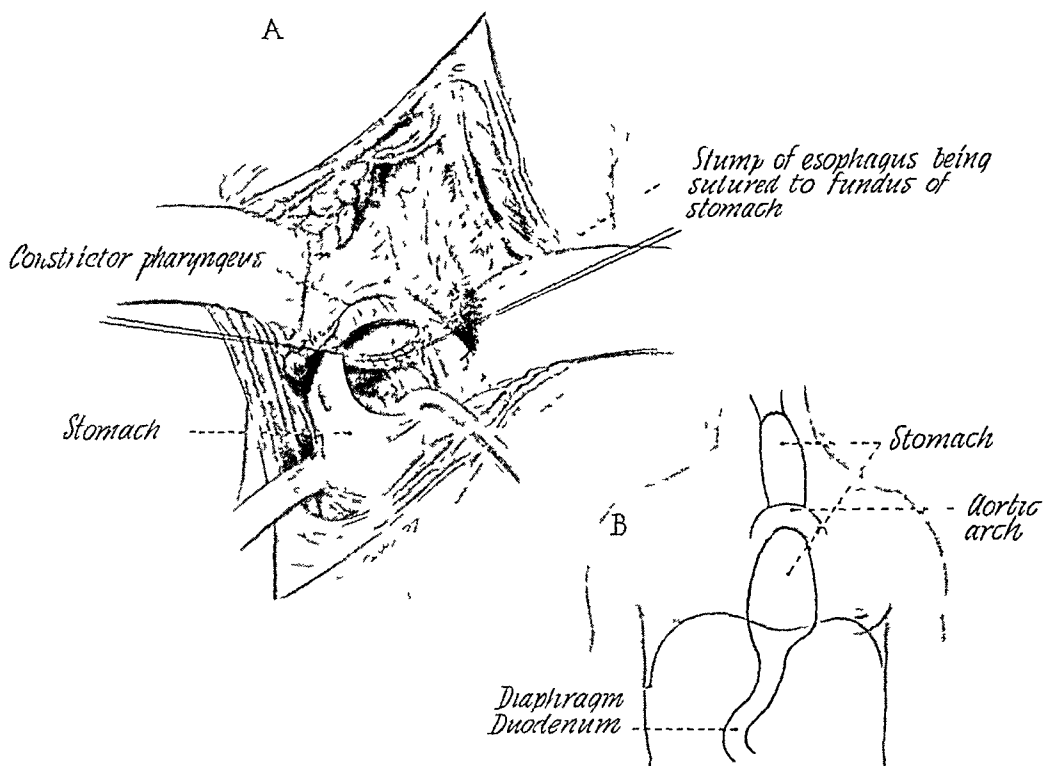


FIG 4—The entire thoracic esophagus has been drawn up into the cervical wound

esophageal branches of the inferior thyroid artery. The esophagus was then pulled out through the reopened cervical incision, which had been lightly closed with a few mattress sutures. Keeping the left gastro-epiploic vessels on the left side and the lesser curvature on the right, the stomach was moved into the thorax. It was brought up *behind* the arch of the aorta in the normal esophageal bed and thence to the dome of the pleural cavity and up into the neck.

The operation was then continued in the cervical region, and the entire thoracic esophagus pulled up into the cervical wound (Fig. 4). We were pleased to find that it was possible to bring the stomach up to the level of the cricothyroid pinch cock. Two small pieces of omentum had been saved to reinforce the anastomosis. A circular incision 2 cm. in diameter was made in the fundus of the stomach which was just below the

most cephalad portion of the stomach, and several bleeding vessels were ligated. The stomach had a slightly bluish appearance, and was not as pink as we are accustomed to see it for an intrathoracic esophagogastric anastomosis. This apical portion of the stomach was sutured to the esophagus just below its junction with the pharynx at the cricothyroid pinch cock. We wished to preserve the pinch cock to prevent regurgitation of gastric contents into the mouth. The anastomosis was then made with interrupted No 0000 silk, first uniting the posterior muscularis of the esophagus to the serosa of the stomach. The esophagus was then amputated and a careful circumferential layer of sutures was placed to unite the esophageal and gastric mucosae together (Fig 5A). Anteriorly the muscularis of the esophagus and the serosa of the stomach were then



5—A A careful three-layer open anastomosis of the stomach and esophagus is made with No 0000 silk
The position of the stomach in the thoracico-cervical region is shown diagrammatically

approximated. A few interrupted sutures were taken to make a third layer of closure, muscularis to serosa, and the omentum which had been saved was further tacked to the anastomosis to reinforce it. The stomach was then fixed to the cervical tissues with interrupted sutures of fine silk. Penrose drains were inserted inferiorly toward the superior mediastinum and superiorly to the region of the anastomosis. The wound was closed in layers with interrupted fine silk, bringing together first the ribbon muscles of the neck, then the platysma and the skin. The thorax was entered, and the stomach was sutured to the superior mediastinal pleura with interrupted silk sutures to seal off the thorax from the cervical region. In fixing the stomach to the adventitia of the descending aorta, one suture struck a branch of the left gastro-epiploic artery and a hematoma, 2 cm in diameter, developed in the gastocolic omentum. The bleeding stopped spontaneously. The diaphragm was closed with interrupted silk sutures, imbricating with running No 1 chromic catgut. The stomach fell posteriorly in the esophageal hiatus and was attached

anteriorly to the diaphragm with fine silk sutures. Drainage tubes were left in the second and eighth intercostal spaces and connected to a closed water-seal drainage system. The wound was washed out with saline. Because of the wide opening of the rib spreaders, the costal cartilage at the sixth and seventh chondral junction had been fractured, so that it was necessary to repair this fracture with two sutures of heavy silk. Closure was effected using No. 1 chromic catgut for the deep muscles, No. 000 chromic for the superficial fascia and silk for the skin. Despite the long, tedious operation (nine and a half hours), the patient was not in shock at the end of the surgery. The blood pressure was 100/60, pulse 100 and respirations 22. Figure 5 shows diagrammatically the position of the stomach at the end of the operation.

The report of the pathologic specimen is as follows: "The gross specimen consists of a resected segment of esophagus which measures 22.5 cm in length. Near one extremity of the specimen the lumen is almost completely occluded by an annular carcinomatous tumor mass which measures 5.5 mm in length. Section through this shows cellular, grayish-pink tumor tissue infiltrating through the thickness of the esophageal wall. The mucosal surface above this point is intact and pinkish gray in color.

Histologic examination of sections taken through the tumor mass described above shows that it is made up of irregular clusters and strands of epithelial cells of squamous type. These form occasional epithelial pearls. There are frequent mitotic figures and hyperchromatic nuclei. Tumor cells are seen within the lumina of small vascular spaces in the muscularis. The diagnosis is squamous-cell carcinoma, Grade III, of esophagus." Angus Wright, M.D., Pathologist

POSTOPERATIVE COURSE

Oxygen was given per nasal catheter with CO₂ inhalation every half hour till the patient was awake and then every 2 hours. The patient was turned from one side to the other at two-hour intervals. Demerol in 50 mg doses was used for pain and he was placed in Fowler's position as soon as he was awake and could cough. Penicillin, 50,000 units, every 3 hours, and streptomycin, 1.0 Gm daily, were administered, intramuscularly. A Levine tube was placed in the stomach and connected to a Chaffin-Pratt suction machine for 24 hours to prevent regurgitation of stomach contents into the pharynx. The anterior thoracic intrapleural drainage tube was clamped 4 hours after operation and 100,000 units of penicillin in 30 cc normal saline were injected into the pleural cavity. The clamp was released after 6 hours.

The temperature was 102° (rectal), pulse, 120, and respirations, 28 on the first postoperative day. The left lung was expanded and signs of patchy atelectasis in the right lower lobe were present on the second postoperative day. By means of a rubber catheter, passed without anesthesia transnasally into the right main bronchus, 10 cc of thick glue-like mucus were aspirated. This procedure was repeated 5 times during the next two days until the right lung was entirely clear. The temperature fell to 100° (rectal), pulse, 90, respirations, 22 on the third postoperative day, the drainage tubes were removed from the left chest and the patient was allowed out of bed. Intravenous fluids consisting of 2,000 cc of 5 per cent glucose in water and 1,000 cc of 5 per cent glucose in saline were given daily. On the fourth postoperative day, fluids were started by mouth, one ounce of water every hour. Swallowing was difficult at first as there was bulging of the left side of the neck, apparently from dilatation of the stomach. The patient coughed with this dilatation, which was interpreted as evidence of pressure on the trachea. The wounds healed per primam and the drains were removed from the neck on the eleventh postoperative day.

Roentgen studies were made 15 days after the operation. Figure 6 shows barium outlining the stomach, which has a retrocardiac position in the thorax and is located in the neck in the esophageal bed. The lung fields are otherwise normal. Figure 7A demonstrates a detail of the gastric outline in the upper thorax, as shown by the introduction

of barium The aortic arch constricts the posterior-lying stomach, and partly acts as a cardia Figure 7B illustrates the straightening out of the duodenum beneath the stomach, which is almost entirely intrathoracic in position The satisfactory emptying of the duodenum into the jejunum is seen in Figure 8

The coughing, associated with eating, gradually subsided and the patient was discharged on the sixteenth postoperative day on soft diet, 2,570 calories with proteins, 140, carbohydrates, 199, and fats, 123 He continued to gain in weight (10 pounds) and strength The swallowing improved so that there was only an occasional coughing following the ingestion of food Esophagoscopy three months after the operation showed a slight stricture of the anastomosis at the level of the cricopharyngeus, which admitted a No 30 French dilator readily



FIG 6

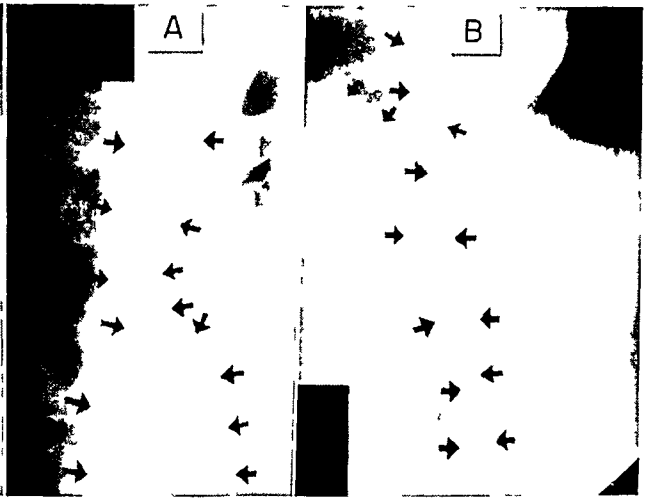


FIG 7

FIG 6—Upper gastro-intestinal series taken 15 days after operation The stomach lies behind the heart in the thorax and extends up into the neck in the esophageal bed The lung fields are clear The sixth rib has been resected

FIG 7—(A, left) Detailed barium study of the stomach in the upper thorax demonstrates the constricting effect of the aortic arch on the stomach

(B, right) The pylorus of the stomach is near the diaphragm and the duodenum is straightened out

DISCUSSION

The success of this operation is dependent upon attention to many details which we have emphasized for the surgical resection of carcinoma of the upper third of the thoracic segment of the esophagus¹⁰ In addition, certain other points should be mentioned The extensive mobilization of the stomach, necessary to bring it up into the neck, is effected by freeing the entire stomach, pylorus and duodenum Greater care must be observed in preserving the blood supply to the stomach and duodenum than for an intrathoracic mobilization of the stomach This can be done by (1) preserving a generous cuff of omentum along the greater curvature, (2) freeing the pylorus and the duodenum by blunt dissection, (3) avoiding tension and torsion on the stomach To mobilize the duodenum, one may excise the peritoneum lateral to the duodenum, as advocated by Priestley and Kumpuris¹¹ for the performance of an esophagoduodenal anastomosis in total gastrectomy The

ligation of the individual branches of the left gastric artery and vein permits more stretch to the lesser curvature so that the stomach is a straight tube, rather than a comma-shaped curved organ. Greater length of the gastric tube can be obtained by placing it behind the arch of the aorta in the esophageal bed. This will give an additional 2 to 4 cm. of length to the stomach. Besides this, the aortic arch will constrict the posterior-lying stomach and tend to prevent the regurgitation of fluid cephalad to the aortic arch when the patient is lying down (Fig 7A)



FIG 8—The barium is seen to enter the jejunum freely from the straightened-out duodenum

After making the cervical anastomosis, the omentum, brought up into the neck, will help reinforce this union. A closure of the mediastinal pleura about the stomach at the thoracic inlet will tend to isolate the cervical regions from the thorax. If a breakdown in the anastomosis occurs, then the drainage will escape through the cervical tissues, along the track made by the cervically placed Penrose sheath drains. Even though the drainage in our case was nil,

we left these drains in 11 days to form a definite track for escape of infected fluid from a possible leak in the anastomosis. The anastomosis in our case healed per primam.

It is advisable to preserve the cricopharyngeus muscle, if possible, in order to prevent regurgitation of gastric juice into the pharynx and thus avoid pharyngeal and oral ulcerations. With this muscle intact, no regurgitation of gastric juice was experienced in our case. As mentioned before, the placing of the stomach behind the arch of the aorta probably also tended to lessen the regurgitation. The cough following the ingestion of food, soon after operation, may have been due to (1) pressure of the stomach on the trachea, (2) cricopharyngeal spasm, or distortion of this muscle, possibly traumatized by suture, or (3) actual stenosis at the esophagogastric junction. The fact that this symptom, which was troublesome soon after operation, gradually improved makes us believe that it was mainly due to the first two causes. It is true that there was some stenosis at the anastomosis (No. 30 French), yet we have observed patients with stenosis much smaller than this who could swallow fluids and soft solids without regurgitation and cough.

The question occurs: will it be possible always to mobilize the stomach sufficiently to bring it up into the neck for anastomosis? This question cannot be answered at the present time. The stomach in the present case was of average size. It is true that great difficulty might be encountered in obtaining sufficient mobilization of a greatly contracted stomach. The gastro-intestinal series may throw some light on this problem. With the use of very thin barium, it may be possible to outline the size of the stomach. Gastric barium studies in our case indicated a normal-sized stomach. A greatly contracted gastric shadow would probably contraindicate this procedure. It is wise not to injure the blood supply to the esophagus until the diaphragm has been opened and the size of the stomach determined accurately. If it was proved impossible to mobilize the stomach well into the neck, a high thoracic gastrostomy could be performed and the defect bridged by a skin tube. The anticipated result of such a procedure would be less desirable than could be expected for the one-stage operation presented here.

In addition to careful preoperative preparation of the patient, meticulous surgical technic and skillful anesthesia, so administered as to prevent hypoxia and shock, the postoperative care is extremely important.¹⁰ The routine use of penicillin and streptomycin have made mediastinal and intrapleural infection less of a problem for the resection of carcinoma of the esophagus, regardless of the location. Besides the maintenance of nutrition and fluid and salt balance during the early postoperative period, the prevention and management of postoperative pulmonary complications is of prime importance. The success of the operation often hinges on this one factor. In our case, despite diligent precautions, a patchy atelectasis of the right lower lobe developed. We employed catheter aspiration of the trachea and bronchi^{12, 13} six different times during the second and third postoperative days. Certainly without this

meticulous attention to the bronchial toilet, all our previous hard work on this case would have been in vain

The operation of Bricker and Burford fulfills the requirement of resection of extensive carcinoma of the cervical esophagus in which the upper thoracic esophagus is also involved. Actually they performed a bilateral neck dissection at the first stage, so that a more thorough removal of carcinoma in the lymphatic channels was effected. Their operation has the inherent disadvantage of all multi-stage operations for cancer in which a considerable period of time is required for the completion of the plastic procedures. The carcinoma may recur soon after the skin tube is completed. In the time necessary to fashion the tube, the patient has been unable to swallow and has been fed by a gastrostomy. The one-stage operation we have presented is superior from this point of view in that the patient can swallow soon after the operation has been completed. Thus, even if recurrence of the carcinoma develops, successful palliation has been promptly effected. The disadvantage of the one-stage operation lies in the fact that a bilateral neck dissection was not performed. This might be done as a preliminary operation, at which time the operability of the carcinoma could be determined. Whenever the carcinoma cells extend from the esophageal mucosa through the muscularis and are in approximation with, or invading, the adjacent structures (a common finding in these cases), permanent cure cannot be expected and only palliation is effected. In our case the carcinoma cells had extended through the esophageal muscularis, so that recurrence may be anticipated. A great deal more experience will be necessary for the true evaluation of the multi-stage and the single-stage procedures.

SUMMARY

1 A case of successful one-stage resection of carcinoma of the cervical esophagus with a subpharyngeal esophagogastronomy has been presented

2 The surgical problems involved in the resection of carcinoma of the cervical esophagus and the cervical esophagogastric anastomosis have been discussed

3 This operation offers hope for one-stage resection of the tumor and immediate return of swallowing to these miserable patients with carcinoma of the cervical esophagus in which there is extensive involvement in the cervical region or an extension of the cancer into the thoracic esophagus

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CERVICAL ESOPHAGOGASTROSTOMY FOLLOWING RESECTION OF SUPRA-AORTIC CARCINOMA OF THE ESOPHAGUS*

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IN THE PAST FEW YEARS partial esophagectomy plus primary intrathoracic esophagogastrostomy has become the operation of choice for removal of carcinomas of the lower two-thirds of the thoracic esophagus. Until recently, however, this technic seemed unsuitable for cancers located in the upper third, that is in the supra-aortic part of the thoracic esophagus.

A few months ago Garlock¹ described a combined cervico-thoracic approach which permits excision of the entire thoracic esophagus and restoration of the alimentary canal by means of a cervical esophagogastrostomy. Garlock's patient died on the morning of the first postoperative day of what Garlock believes were "profound physiological disturbances possibly caused by vagal stimulation." Garlock's technique was employed in the case to be reported, and the description will be given in the operative report.

CASE REPORT

A 61-year-old white male was admitted to the Jewish Hospital of Brooklyn on December 10, 1948, because of difficulty in swallowing for the preceding six weeks. This began as a feeling of heaviness while swallowing and progressed rapidly so that at the time of admission he could not swallow solid food. He could take liquids in small amounts. Solid food or large swallows of liquids seemed to become blocked in the region of the jugular notch and were regurgitated. There was a 7 lb weight loss, but no cough, fever, pain nor change in speech, and with no melena or hemoptysis.

Past History In 1937 amputation of the penis and bilateral inguinal node dissection was performed for carcinoma of the penis. He has had no subsequent difficulty in voiding and no evidence of recurrence. There has been a partial bilateral difficulty in hearing for the past three years.

Physical Examination T 99 B P 124/64 Pulse 68 Resp 20. The patient is a well developed, thin white male. There is no evidence of recent weight loss. The penis has been amputated at its base, the meatus is patent and he voids in a good stream. There are bilateral 6-inch inguinal scars. Remainder of physical examination is negative except for partial deafness. Impression at time of admission: carcinoma of the esophagus. The patient was esophagoscoped and a biopsy taken from a tumor mass in the upper esophagus.

Pathologic Report Tissue from esophagus showed evidence of epidermoid carcinoma.

Roentgen-ray examination of the esophagus by means of a barium swallow revealed a narrowing between the level of the jugular notch and the upper border of the aortic arch. Only a trickle of barium was seen to pass through the constricted area (Fig 1).

Laboratory Data on Admission Blood count: Hgb 88 per cent, RBC 4.35, WBC 7000, 38 per cent polys, 61 lymphs, 1 eosin. Urine: acid, 1.020, trace of albumin. O sugar.

Blood chemical determinations: sugar 85 mg per 100 cc, urea 9 mg per 100 cc, CO₂ 69 vol per cent, chloride 354 mg per cent, prothrombin time normal, phosphorus 3.4 mg per cent, alkaline phosphate 2.2 Bodansky units per cent, total protein 6.2 per

* Submitted for publication, March, 1949.

cent, albumin 3.6 per cent, globulin 2.6 per cent, Mazzini negative. Electrocardiogram was normal.

The patient was prepared with blood transfusions and hydrated with intravenous glucose and saline solutions and the operation performed on December 17, 1948, under endotracheal cyclopropane, ether, oxygen anesthesia. He was placed on the table slightly

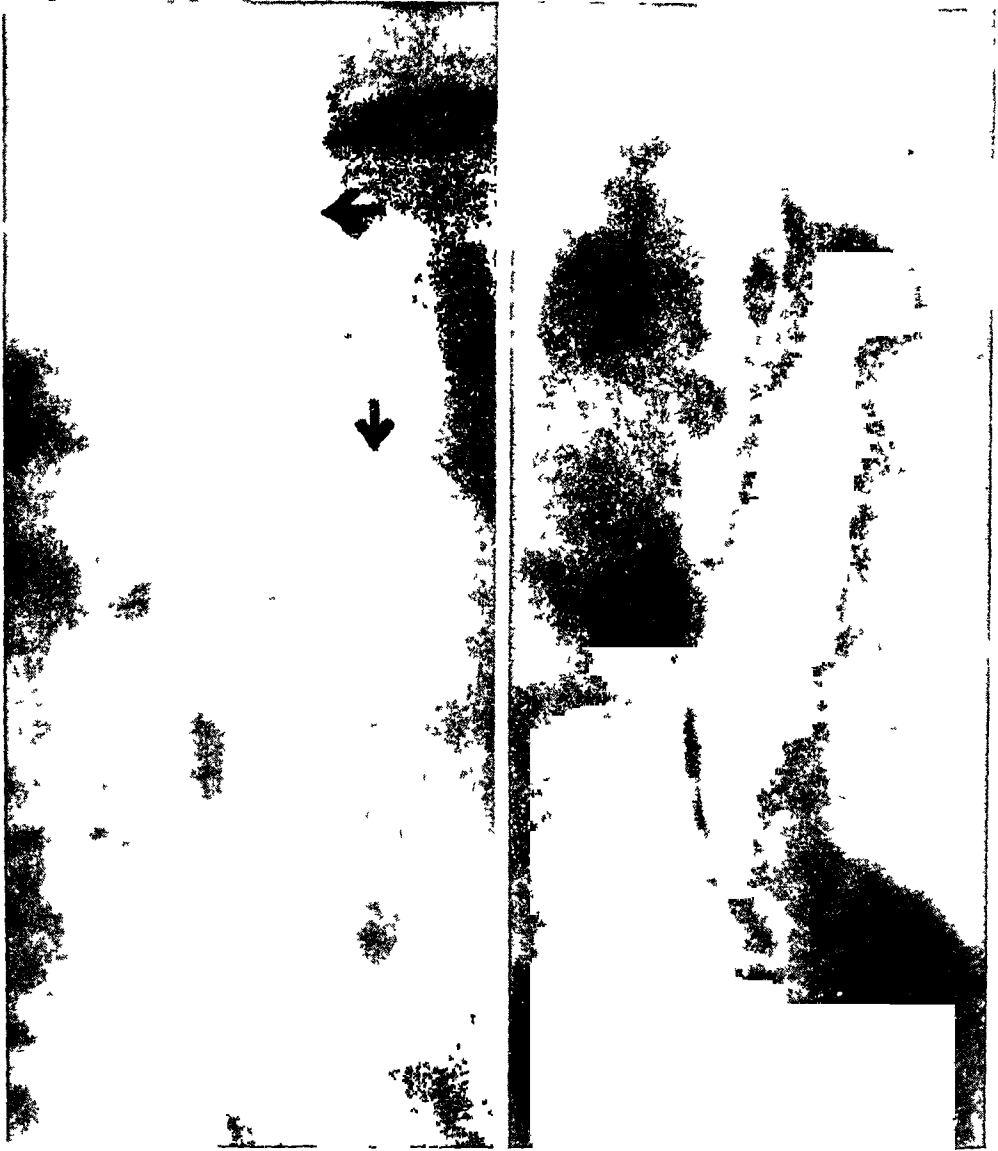


FIG 1—Preoperative esophagogram. Defect in the superior mediastinal segment between the level of jugular notch (arrow) and upper border of aortic arch (arrow).

turned towards his right side, and the whole of the left and left-anterior surfaces of the neck, thorax and upper abdomen exposed and prepared as the operative field. The left arm, wrapped in sterile towels, was supported away from the body at about 45 degrees.

The objective of the first phase of the operation was to determine the operability of the tumor. The incision was made along the anterior border of the left sternocleidomastoid muscle from the level of the hyoid bone to the jugular notch. The muscle was retracted toward the left, and the left lobe of the thyroid toward the right. The middle thyroid vein was ligated and divided, care being taken to leave the lower thyroid artery.

CERVICAL ESOPHAGOGASTROSTOMY

intact The cervical section of the esophagus being exposed, a finger was inserted from the side and introduced into the upper mediastinum in front of the esophagus The tumor, as well as a mass of nodes to the right of it could be palpated and delineated by blunt dissection The tip of the finger could then be gently advanced to the posterior surface of the arch of the aorta (Fig 2) It was found that the tumor could be readily freed from the trachea, and was therefore removable A pad was placed in the upper mediastinum and the incision temporarily closed with clips

The patient was then turned to the full right-side position, and the arm supported diagonally upward and forward An incision was now made along the 6th rib and the rib resected from the costo-vertebral angle to its costal cartilage The pleural space was found to be obliterated by adhesions which were 5 mm thick in some places Only the upper pleural area was in normal condition The adhesions were broken down, partly by extrapleural pleurolysis so that the lung could retract After the rib-spreader was placed in position, the entire left pleural cavity could be freely explored and next the mediastinal

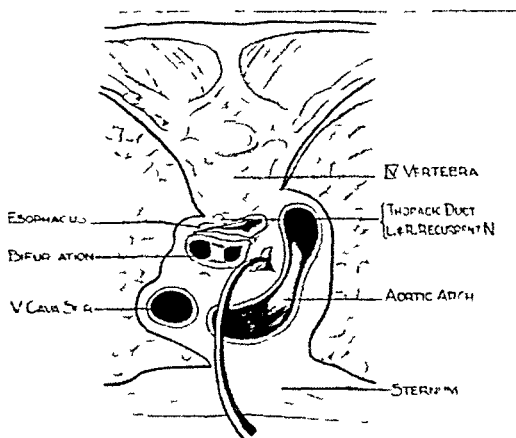


FIG 2—Cross-section at the level of the 4th dorsal vertebra The arrow indicates the paraesophageal space which is explored from the cervical incision in order to determine operability of the tumor

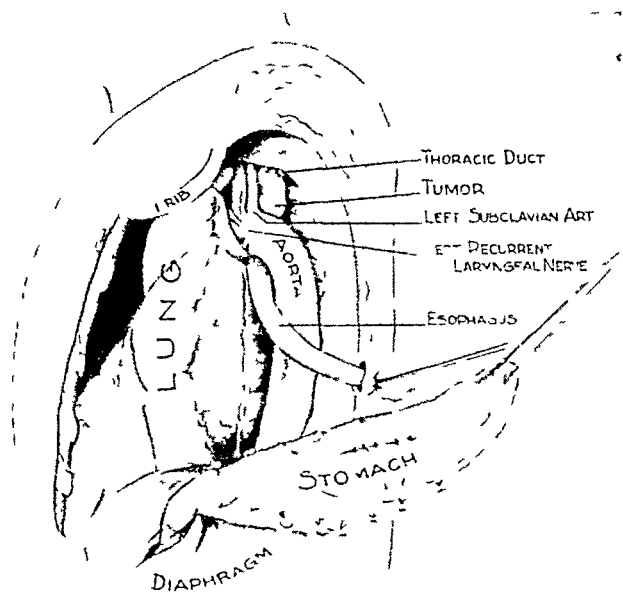


FIG 3—The cardia is transected and inverted after mobilization of esophagus and stomach

pleura attached to the esophagus was incised both above the aortic arch and below it as far as the cardia The pad was then removed from the upper mediastinum The diseased area of the esophagus could then be freed on all sides, without damage to the left recurrent laryngeal nerve or the thoracic duct The left vagus nerve was identified in the upper angle of the wound, the right vagus nerve remained unexposed

The esophagus was then freed along the rest of its length, after the vessels supplying it from the aortic arch and aorta had been divided between silver clips The two Nn vagi were identified below the tracheal bifurcation and cut The phrenic nerve was crushed above the diaphragm and then the diaphragm itself was incised from the hiatus almost up to the lateral chest wall, permitting access to the upper abdominal cavity The stomach was then mobilized in the usual manner after ligation and division of the left gastric artery, the vasa brevia and the left gastro-epiploic vessels The gastro-colic ligament was divided close to its colonic attachment so that its own blood vessels could be preserved for collaterals to the stomach The stomach was cleared of all connections as far as the pylorus

The esophagus was then cut through at its junction with the stomach and the cardia closed with a double row of interrupted silk sutures The open end of the esophagus was tied off and covered by a rubber cap, fixed in position with a strong silk thread which

was left long (Fig 3) By means of a long forceps passed through the cervical incision into the mediastinum the free end of the esophagus was grasped and the entire thoracic esophagus was pulled out through the cervical wound

The uppermost tip of the fundus of the stomach was then equipped with two strong sutures to be used for manipulating the organ The long ends of these sutures were grasped by the forceps, again introduced through the cervical wound, and the stomach was thus pulled upward between the hilus of the lung and the aortic arch In this way the stomach had the aortic arch behind it and the hilus in front of it The transposition of the stomach into the cervical incision was aided by manual support through the open

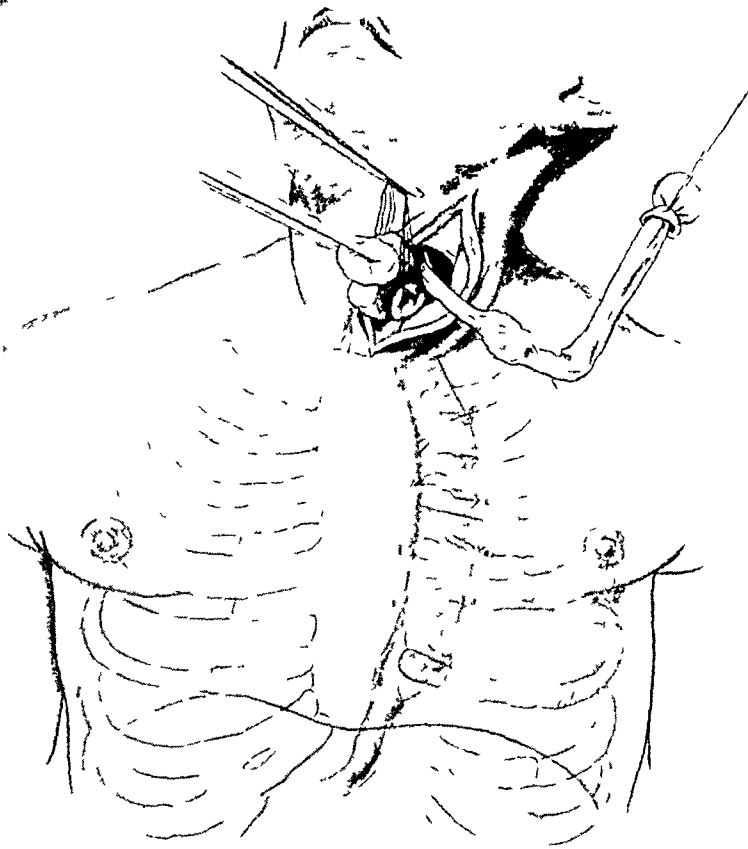


FIG 4—The esophagus is pulled out through the cervical incision The stomach is withdrawn through the lower angle of the same incision and held in this position by 2 guide sutures

chest cavity, and the fundus could readily be brought up to the level of the larynx The stomach was held in this position by means of a clamp attached close to the knots of the holding sutures and resting across the line of the neck incision (Fig 4)

A number of fine silk sutures were used to attach the intrathoracic gastric segment to the mediastinal pleura At the point where the fundus of the stomach enters the neck area the sutures were placed close together so that the line would be air-tight Then the incision in the diaphragm was closed by single sutures and centrally its edges were attached to the adjacent prepyloric region of the stomach Twenty cc of saline containing 100,000 units of penicillin were divided between mediastinum and pleural cavity

A medium-sized catheter was now introduced into the chest cavity via a small incision in the ninth intercostal space at the posterior axillary line The lung was inflated, and the chest incision closed in layers

CERVICAL ESOPHAGOGASTROSTOMY

The patient was then placed on his back, and the cervical incision reopened. The esophagus was transected 2 cm above the upper limit of the tumor, the fundus was incised between the two holding sutures and anastomosis made between it and the upper esophagus remnant by means of a double layer of single sutures of fine silk. After the posterior suture line was finished, the anesthetist passed a Levine tube through the nose into esophagus and stomach. The left lobe of the thyroid was used as a covering to reinforce the front of the anastomosis. Two strips of iodoform gauze were inserted towards the mediastinum, and the neck incision closed in two layers.

The duration of the operation was $3\frac{1}{2}$ hours, and up to the last 15 minutes there were no notable fluctuations in pulse or blood-pressure. There was a moderate fall in blood-pressure during the last quarter hour. A blood transfusion was started just before the first incision, and 1500 cc were given during the operation.

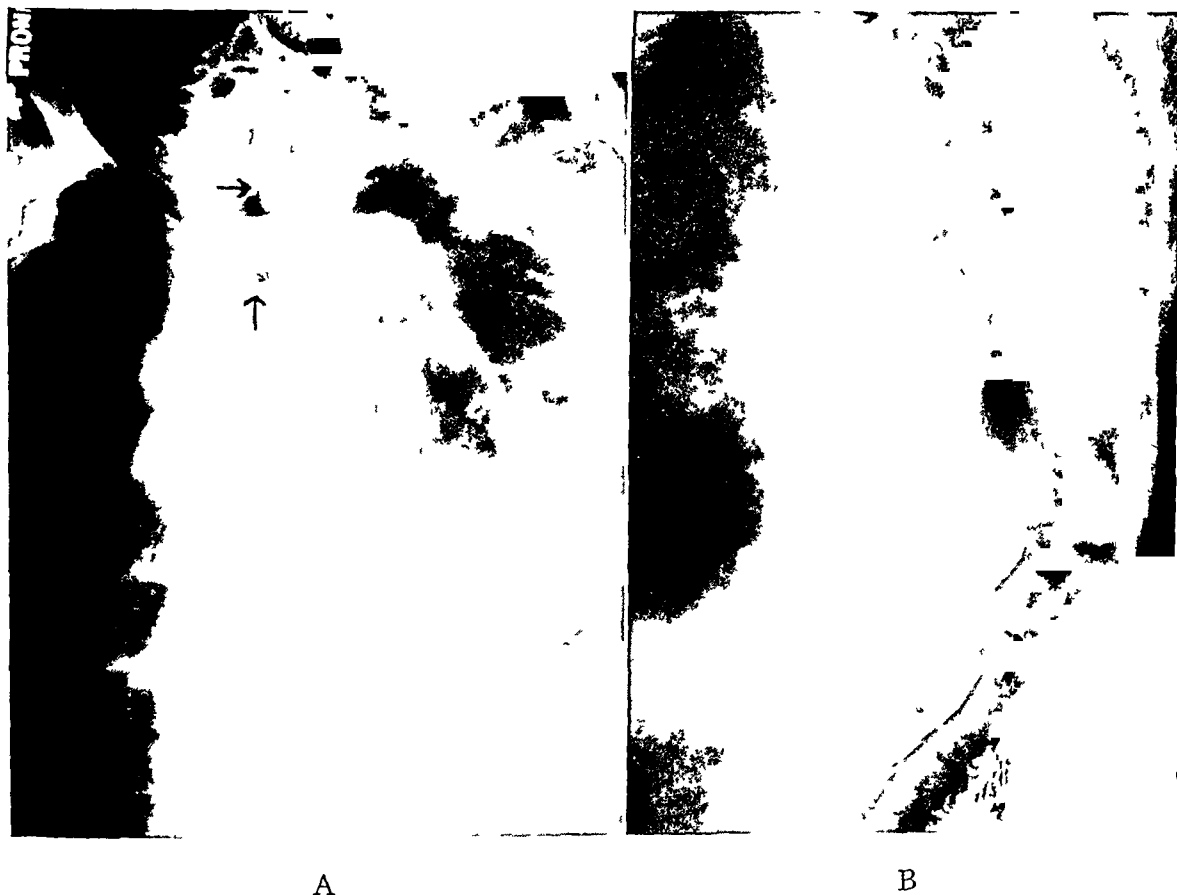


FIG 5 (A & B)—Postoperative roentgenograms after ingestion of barium. The anastomosis (arrow) is visible above the level of the suprasternal notch (Arrow).

After the bronchial secretions had been aspirated, the endotracheal tube was withdrawn and the patient was returned to bed under an oxygen tent. The Levine tube was connected with a Wangenstein suction apparatus, the intercostal catheter with an under-water drainage bottle.

The patient regained consciousness after $1\frac{1}{2}$ hours. There had been no damage to the recurrent laryngeal nerves, as his voice was normal. For a time, daily intramuscular injections of penicillin and streptomycin were given. For the first five days parenteral feeding was used exclusively (2000 cc of 5 per cent glucose solution were given daily and 500 cc of blood every second day). The Levine tube was withdrawn on the fifth day. Oral feeding was begun with 15 cc of milk every hour and after three more days fluids were permitted as desired. From the tenth postoperative day soft diet was given and swallowing proceeded normally. Drainage through the intercostal catheter ceased on

the third postoperative day, and the tube was removed on the fifth day. The gauze drains were withdrawn from the neck wound on the sixth day.

Roentgen-ray films at the bedside on the third, fifth and eighth days after operation revealed clear lung fields on both sides except for a shadow in the lower left area. A tube-shaped air space, corresponding to the situation of the intrathoracic stomach was plainly visible. The patient was out of bed on the sixth postoperative day.



FIG 6—Postoperative roentgenogram of the cervical esophagogastrostomy. Anastomosis and suprasternal notch marked by arrows.

Attacks of expiratory dyspnoea very similar to bronchial asthma occurred from the second to the eighth day after operation. These spells lasted from 10 minutes to as long as three hours, accompanied by the characteristic asthmatic wheezing, but uninfluenced by adrenalin and atropin injections. There were no further attacks after the eighth day. During the first few days after operation the pulse rate remained at from 100 to 120, but

returned to normal on the seventh day. For the first ten days the respiratory rate was 22 and 26.

Pathologist's Postoperative Report The specimen consists of resected portion of esophagus which is already opened and measures 18 cm in length. One and one-half cm from one end there is a firm elevated nodular sub-mucosal area which tapers into a constricted portion. This constriction is 4 cm from one end. Six cm from this end the mucosa is replaced by yellow tan, firm papillary-like tissue which is continuous with the submucosal layer described above. In an area from 2 to 8 cm from one end of the esophagus the submucosal tissue is hard and nodular. The mucosa in this area is a greenish red and is firmly adherent to the submucosa. The remainder of the mucosa is tan, gray, and is freely movable. Two lymph nodes 1 cm in diameter are found at the central portion of the esophagus.

Microscopic Examination In one area the mucosa is ulcerated. The tumor consists of nests of ovoid or polygonal cells of varying size and shape. In many cells the nuclei are hyperchromic and in a few mitotic figures are present. There are extensive foci of necrosis. The lymph nodes show extensive pigmentation, but no involvement by tumor.

Roentgen-ray pictures taken four weeks postoperative show the new location of the stomach with the esophagogastrostomy above the level of the supra sternal notch (Figs 5, 6) (See footnote, page 30.)

COMMENT

In our technic of operation there were a few minor deviations from Garlock's description. We resected the sixth rib instead of the seventh in order to have a better approach to the supra aortic space, where preservation of the recurrent nerves and the thoracic duct demand careful dissection and hemostasis under adequate visualization.

No attempt was made to anchor the upper end of the transplanted stomach to the areolar tissue of the jugular notch. The success of the entire procedure must depend in large part upon maintaining an adequate blood supply for the mobilized stomach. We therefore avoided placing any sutures (which might occlude vessels unnecessarily) in the stomach wall, particularly as there was no evidence of increased tension upon the anastomosis.

This "drag" on the anastomosis which is often mentioned in the papers dealing with esophago-gastriostomy seems to be somewhat overstressed. There are cases in which at the end of the operation some tension on the anastomosis is evident, but even in these the usual atonia caused by vagotomy will neutralize the drag in a short time. In one of our patients (carcinoma of the middle third) the anastomosis was under considerable tension. As this patient had had a previous esophagogastrostomy for cardiospasm, the stomach was simply too short to allow relaxation of the tension, although the organ had been well mobilized. When, three weeks following the operation, an esophagogram was taken, we were surprised to find the fundus of the stomach in the dome of the pleura, its cranial end at a higher level than the anastomosis.

Preservation of the cervical and upper thoracic portions of the *Nn vagi* is obviously a prerequisite for a satisfactory outcome. As noted in the description of the operation, we cut the nerves well beyond the level of the bifurcation of the trachea so as to save those branches joining the pulmonary plexus.

Garlock believes that "vagal stimulation" was the cause of death in his patient. But it is questionable, whether a protracted vagal reflex ever does occur. During the operation mentioned by Garlock, pulse, blood pressure and respiratory rate remained undisturbed. There was thus no evidence of hyperstimulation of the vagi while the dissection in the vicinity of the nerves was being performed. It seems unlikely that any marked degree of irritation of the vagi would develop after completion of the operation.

On the other hand late fatal effects are well known as a consequence of vagal *paralysis*. In fact, bilateral vagotomy at a high level is always fatal in



FIG 7



FIG 8

FIGS 7 and 8—Photographs of patient 6 weeks after operation. Neck incision and thoracic incision visible.

experimental animals, as is confirmed in the physiological literature. In these experiments bilateral vagotomy was routinely done at the cervical portion of the nerves, and the simultaneous paralysis of the laryngeal recurrences was believed to be the cause of the fatal pneumonia. Other theories emphasize the inability of glycogen synthesis in the liver following vagotomy which in turn may seriously impair the nutritional condition of the heart muscle. In experiments on dogs, we² found sufficient proof to assume that maintenance of the pH equilibrium in the blood is dependent on intact cervical portions of the vagi nerves. After bilateral vagotomy an irreversible and therefore fatal acidosis by CO₂ accumulation in the blood developed.

Attempts to replace the entire thoracic esophagus by the mobilized stomach are not new. As far back as 1920 Kirschner³ was successful in performing a cervical esophagogastrostomy on a patient with cicatricial stenosis of the mediastinal part of the esophagus. No resection, however, was done. Kirschner divided the stomach close to the cardia and performed an anastomosis between cardia and jejunum. The stomach was then mobilized in the same way as has become today's routine procedure, and was brought up to the neck through a subcutaneous tunnel on the anterior chest wall. The cervical esophagus was exposed and connected with the fundus of the stomach by side-to-side anastomosis. The patient survived. Kirschner thought it an advantage to avoid the transpleural route. H. Kuemmell Jr.⁴ advised a similar method. He freed the thoracic esophagus through the hiatus esophagus and a left cervical incision by blunt and blind dissection. The stomach was then devascularized according to Kirschner and pulled up to the neck. None of Kuemmell's patients survived.

The first case of successful cervical esophagogastrostomy following resection of an upper third cancer was reported by Sweet⁵ in December, 1948 (Operation on October 28, 1947). Sweet started with the thoraco-abdominal part of the operation, turned the patient on his back and performed the anastomosis from a combined thoraco-cervical incision. He thought it necessary to remove the mesial part of the left clavicle, the prominent corner of the manubrium of the sternum, and the anterior half of the first rib. A previous attempt to pull the stomach up through the apex of the thorax into the base of the neck had apparently failed because of insufficient room to perform an anastomosis. It may be assumed that Sweet had to deal with an abnormally narrow aperture. We did not experience any difficulty in bringing the stomach through the aperture. There was even room enough to place two packs beside the end of the stomach. This is understandable, for we know that the lower lobes of the thyroid gland often grow down into the upper mediastinum without causing pressure symptoms. In the average case Garlock's procedure seems to be preferable, because it is the simpler one.

Data as to the after effects of cervical esophagogastrostomy are beginning to be recorded. Garlock himself interpreted the significance of the fatal outcome of his case as probably connected with some changes in the vagal mechanism secondary to operation. Sweet noticed that turning his patient on the left side was followed by rapid pulse and marked fall in blood pressure. Both signs disappeared when he was turned back again. This was thought to be caused by stimulation of the carotid sinus.

In our case a postoperative complication was an asthmatic condition lasting for five days, and uninfluenced by atropin and adrenalin. Asthmatic attacks had not occurred previously. The expiratory dyspnea itself was not serious, but the accompanying cough—though rather unproductive—caused regurgitation of gastric content. Factors probably responsible for this are the high level of the anastomosis adjacent to the pharynx, the absence of a sphinc-

ter mechanism, and the atonic state of the stomach because of vagotomy. Thus the stomach is exposed to the oscillations of the intrapleural pressure which becomes strongly positive during the cough effort. The relation of the attacks of bronchial asthma to the operative procedure is problematical. Vagal and sympathetic nerves both are said to participate in the innervation of the muscles of the bronchial wall. Surgical treatment of bronchial asthma has been tried by means of sympathectomy and vagotomy. The reported percentages of alleged improvements are about the same, whether sympathectomy or vagotomy was performed.

SUMMARY

A case of cervical esophago-gastrostomy following resection of a supra-aortic carcinoma of the esophagus is reported. The satisfactory outcome of the operation indicates the justification of a combined cervico-thoracic approach as recommended by Garlock.

The rôle of the Nn vagi in postoperative disturbances is discussed.

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(Footnote to case report ending on page 27.) The last follow-up examination occurred June 20, 1949. Normal swallowing function (confirmed by roentgenogram) was noted. General condition is satisfactory.

SURGICAL TREATMENT OF DUODENAL ULCER — COMPARISON OF RESULTS WITH AND WITHOUT VAGOTOMY*

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WE ARE REPORTING the results of surgical treatment of 174 cases of intractable duodenal ulcer. The first half of the series had gastric resections or gastro-enterostomies and the second half had vagotomies with pyloroplasty or gastro-enterostomies. Both series are similar in respect to average age, duration of symptoms, preoperative complications and severity of the disease. The same two surgeons performed the operation in both groups. The period of study was from January, 1942, to January, 1948.

TYPE OF OPERATION

The first 87 patients in the series were subjected to gastric resection or gastro-enterostomy. Sixty-seven of these had the distal two-thirds of their stomachs resected and continuity restored by a short-loop retrocolic gastro-jejunostomy, with the distal end of the jejunum directed to the greater curvature of the stomach. Hofmeister's modification of the posterior Polya technic was employed.

Twenty patients were treated by posterior gastro-enterostomy with the jejunal loop attached to the stomach in an antiperistaltic direction. The cases selected for gastro-enterostomy were usually obstructing ulcers in older patients, active ulcers in patients whose condition was such that the risk of resection was too great, or penetrating ulcers in which the technical difficulties of resection would have increased the risk.

The second half of the series is composed of 87 consecutive cases in which transabdominal vagotomy was employed in conjunction with either pyloroplasty or gastro-enterostomy. The pyloroplasty consisted merely in longitudinal division and transverse suture of the pylorus, occasionally with excision of an ulcer on the anterior wall of the duodenum. Gastro-enterostomy was performed by the same technic as in the first series.

INDICATIONS FOR OPERATION

Patients with duodenal ulcer were not operated upon unless they proved intractable to medical management. The indications for operation were the same in the second group as in the first (Table I).

COMPARISON OF THE POSTOPERATIVE FOLLOW-UP

Since none of the patients in the second group have been followed longer than 18 months, care was taken to disregard any symptoms in the first group which appeared more than 18 months after operation. Thus, if a patient had

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had a gastric resection and was well at the end of one year, he would be classified in this study as well, even if he developed a marginal ulcer two years later

In the first group frequent feedings and antacids were advised and smoking and drinking were prohibited, whereas the patients subjected to vagotomy were given no dietary or medical management after the sixth week and were allowed to smoke or drink if they so desired

A factor which may influence the statistics is the fact that the patients subjected to vagotomy were questioned routinely about diarrhea and vomiting. If the patient vomited only once or twice or had two or three stools a day, it

TABLE I

	Gastric Resection or G. E.	Vagotomy with Pyloroplasty or G. E.
Total consecutive cases	87	87
Total followed cases	76	83
Duration of follow-up	5 to 18 mo av — 11 mo	5 to 18 mo av — 14 mo
Average age	44.1 yrs	47.3 yrs
Duration of symptoms	11.9 yrs	12.5 yrs
Duodenal ulcer demonstrated at operation	87	87
Intractable epigastric pain	87	87
Night pain	20	19
Hemorrhage	29	29
	(Multiple 15)	(Multiple 9)
History of perforation	6	8 (Multiple 2)
Pyloric obstruction	29	27

was recorded, whereas minor episodes of diarrhea or vomiting which occurred after gastric resection might not have been recorded at the time and might subsequently have been forgotten by the patient

POSTOPERATIVE COURSE

In general, the postoperative course of the patients with vagotomy and pyloroplasty or gastro-enterostomy was little different from that of the patients with gastric resection or gastro-enterostomy alone. The hospital mortality was lower in the patients subjected to vagotomy than in the first group. There were two deaths after gastric resection and one after gastro-enterostomy alone compared with only one death in the patients with vagotomy.

PERSISTENCE OR RECURRENCE OF ULCER PAIN

There was a striking difference in the two groups regarding control of ulcerlike pain. Ulcerlike distress often persisted after gastric resection or after gastro-enterostomy and required dietary management or antacids but was rarely observed after vagotomy.

TABLE II—*Recurrence of Ulcer Pain Since Operation*

Resection or G. E.		Vagotomy and G. E. or Pyloroplasty	
Yes	18	Yes	4
No	55	No	79

PERSISTENCE OF ABDOMINAL PAIN OTHER THAN ULCERLIKE PAIN

All types of pain, except ulcerlike distress, are included in this category and are about equally common in the two groups. Incisional pain was the commonest. Lower abdominal pain, perhaps referable to the colon, was observed in both groups but was less common in the patients subjected to vagotomy.

TABLE III—*Abdominal Pain Other Than Ulcer Pain Since Operation*

Resection or G. E.		Vagotomy and G. E. or Pyloroplasty	
Yes	20	Yes	20
No	55	No	65

VOMITING

Only two of the patients subjected to pyloroplasty or gastro-enterostomy coupled with vagotomy vomited enough to cause concern. Mild vomiting is defined as not over five times since operation, severe as more than five times. The severity of the vomiting in the first series cannot be estimated accurately because the number of times that the patients vomited was not recorded at the time and memory is not reliable.

TABLE IV—*Vomiting Since Operation*

Resection or G. E.		Vagotomy and G. E. or Pyloroplasty	
Yes	7	Yes Repeatedly	2
		Occasionally	15
		(1 to 6 times a year)	
No	66	No	66

DIARRHEA

Only two patients subjected to vagotomy had troublesome diarrhea, which persisted for more than five months. Five patients in the first group complained of diarrhea of varying degrees of severity. Constipation was also a complaint in a number of cases in both groups. Transitory diarrhea was seen more often in the patients with vagotomies than in the first group.

TABLE V—*Diarrhea Since Operation*

Resection or G. E.			Vagotomy and G. E. or Pyloroplasty	
Yes	5	Yes	2	(5 to 10 stools daily)
			11	(Transient for 6 weeks after operation)
			17	(Occasionally mild—1 to 5 stools daily)
		Total	30	
No	67	No	53	

FEELING OF WELL-BEING

Table VI refers to all complaints referable to any system of the body and includes such symptoms as backache and headache. The question was designed

to evaluate the status of the patient as a whole rather than that of the gastrointestinal tract. The patients with vagotomies had fewer complaints than those in the first group. There appeared to be little difference in the two groups as to the length of time before returning to work.

TABLE VI—*Do You Consider Yourself Well?*

Resection or G E		Vagotomy and G E or Pyloroplasty	
Yes	48	Yes	58
No	20	No	19
Improved	2	Improved	4

DEMONSTRABLE RECURRENT ULCERATION

Two of the three demonstrable jejunal ulcers which occurred in the gastric-resection, gastro-enterostomy group occurred after resections. Three of the four hemorrhages in this group occurred after gastro-enterostomy.

In only one case in the vagotomy group has there been any objective evidence of recurrent ulceration demonstrable by either roentgen ray, gastroscopy, or by such clinical signs as hemorrhage or perforation. This patient was classified at the end of five months as a failure because ulcerlike pain had persisted, unrelieved by gastro-enterostomy and vagotomy. Eight months after operation a jejunal ulcer was demonstrated. Three additional vagus fibers were found, divided and confirmed by histologic examination. The pain which before reoperation had required morphine was relieved at once, but it recurred within three weeks. The gastro-enterostomy was taken down, the jejunal ulcer excised, and a pyloroplasty was performed. After operation the insulin-tolerance test showed clear evidence that the vagotomy was still incomplete. The patient's symptoms have been controlled by a course of roentgenotherapy to the stomach, enterogastrone, antacids and diet. The patient's hypersensitive personality, and his symptoms, suggesting a dump syndrome, even with gastro-enterostomy, influenced our decision to perform a pyloroplasty rather than to resect the stomach.

TABLE VII—*Objective Evidence of Recurrent Ulceration*

Resection or G E		Vagotomy and G E or Pyloroplasty	
Proved jejunal ulcer 2 after gastric resections 1 after G E	3	Proved jejunal ulcer	1
Hemorrhage 1 after resection 3 after G E	4	Hemorrhage	0

EVALUATION OF RESULTS

The criteria used in evaluating the results were shown in Table VIII. Although the group of cases subjected to gastro-enterostomy alone is

small, the difference between the results obtained in this group and those following gastro-enterostomy combined with vagotomy is striking enough to indicate that the excellent results obtained following gastro-enterostomy and vagotomy are not attributable to the gastro-enterostomy alone *

TABLE VIII

Excellent	— 100% normal health from gastro-intestinal standpoint
Satisfactory	— No ulcer distress gastro-intestinal symptoms so mild that they do not interfere with work, no special diet or medication recommended or taken
Improved	— No ulcer distress fewer gastro-intestinal symptoms than before operation, but diet and/or medication have been used to control symptoms
Failure	— Persistence of ulcerlike distress or development of other gastro-intestinal symptoms sufficiently severe to constitute a disability

The results obtained following gastric resection alone and following G E alone are shown in Table X

DISCUSSION

Some surgeons performing 100 operations for duodenal ulcers will perform 50 gastric resections and 50 gastro-enterostomies whereas others may perform 90 resections and 10 gastro-enterostomies. The reasons for selecting one operation or the other depend on the type of ulcer, the condition of the patient and the risk of operation. In evaluating the efficacy of a new procedure, it is not fair to compare it with only a selected group of cases

TABLE IX—*Comparison of Results in 156 Cases Followed From 5 to 18 Months After Operation*

Operation	Excellent	Satisfactory	Improved	Failure
Vagotomy with gastro-enterostomy or pyloroplasty 83 followed cases*	78%	11%	5%	6%
Gastric resection, 57 cases	60%	10%	4%	26%
Gastro-enterostomy 16 cases				
Total 73 followed cases				

treated by gastric resection. For this reason the results obtained following vagotomy combined with a shunt operation should not be compared with the results obtained following gastric resection alone or following gastro-enterostomy alone, but should be compared with an equal number of consecutive cases in which the patients were operated upon by the old technics, including both gastric resections and gastro-enterostomies.

If a surgeon who is accustomed to performing gastric resections for duodenal ulcer begins to employ vagotomy, his tendency is to employ vagotomy at first in the milder cases and to rely on time-tested gastric resection to control the complicated ulcers. Consequently, he may employ vagotomy in some cases in which the objective findings are not proportionate to the subjective, and use it in a selected group of cases whose symptoms are more

* There was no significant difference in the results following vagotomy and gastro-enterostomy as compared with vagotomy and pyloroplasty

the result of functional disorders than of organic disease. Since vagotomy does not benefit functional gastric distress or symptoms due to gastritis, he may find that the results in his selected group of cases are poor.

The cases reported here are not selected but are consecutive. After experience in the technic had been gained by operations on a number of jejunal ulcers, the decision was made to employ vagotomy in the treatment of all duodenal ulcers, and from that time no further gastric resections were employed. Nor were vagotomies employed in the treatment of duodenal ulcer during the period of time that gastric resections were being done. For these reasons both series represent a consecutive, not a selected, group of cases.

In this series the criteria for operation, the severity of the disease and the surgeons performing the operations were the same. The period of follow-up is the same and the percentage of patients followed is comparable. Although the series is small, the differences in results appear to be significant.

TABLE X

Operation	Excellent	Satisfac- tory	Improved	Failure
Gastric resection, 57 cases	67%	10%	4%	19%
Gastro enterostomy, 16 cases	38%	6%	6%	50%

The mortality rate for the vagotomy group is lower than for the group treated by gastric resection or gastro-enterostomy alone. The side effects following vagotomy were of minor importance and were comparable, in most respects, to the side effects following gastro-enterostomy without vagotomy. Even those patients who developed side effects following vagotomy were glad that the operation had been performed and were well pleased with their improvement. Persistence of the symptoms of ulcer and demonstrable recurrences of ulcer were much lower in the vagotomy group. Finally, the number of patients who considered themselves entirely well and the number of patients whose results were objectively classified as excellent were higher in the group subjected to vagotomy.

SUMMARY

1 A series of 174 cases of intractable duodenal ulcer treated by various types of operation is reported.

2 This series is composed of two groups of 87 patients each. In the first group 67 patients were treated by gastric resection and 20 by gastro-enterostomy. In the second group all patients were treated by pyloroplasty or gastro-enterostomy coupled with vagotomy.

3 The two series are similar in respect to average age, duration of symptoms, preoperative complications and severity of the disease. The same two surgeons performed all operations in both groups. The mortality rate in the vagotomy series was 11 per cent as compared to 34 per cent in the patients subjected to gastro-enterostomy or gastric resection.

4 On the basis of our experience, vagotomy with gastro-enterostomy or pyloroplasty has the following advantages over gastric resection or gastro-enterostomy

- a a lower mortality rate
- b a lower incidence of demonstrable recurrent ulceration
- c a lower incidence of recurrent gastro-intestinal hemorrhage
- d a lower incidence of recurrent ulcer pain
- e a lower incidence of abdominal pain of all types

5 Vagotomy with gastro-enterostomy or pyloroplasty has the following disadvantages

- a a possible greater incidence of transitory postoperative vomiting
- b a probable greater incidence of transitory postoperative diarrhea

6 Although the results following gastric resection are superior to those following gastro-enterostomy, even the selected patients (67 of 87) whose stomachs were resected had a significantly higher mortality and morbidity after operation than did those subjected to vagotomy coupled with gastro-enterostomy or pyloroplasty

7 The side effects of vagotomy have been few and mild

CONCLUSION

In the first 18 months after operation, vagotomy, in conjunction with gastro-enterostomy or pyloroplasty, has given better results than gastric resection or gastro-enterostomy alone

✓
"CATEGORICALLY INOPERABLE" CARCINOMA
OF THE BREAST*

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SUCCESSFUL TREATMENT of cancer of the breast can only be accomplished by radical mastectomy This procedure today is essentially the same as that described by Halsted Many technical variations have appeared throughout the years, but with little if any improvement in clinical results

For the most part, the procedure of radical mastectomy has been advised for all patients in which the operation was a technical possibility

In general, the criteria of operability have been

- 1 Movable primary tumor
- 2 Limitation of the metastases to the axilla of the same side as the primary tumor (checked by roentgenograms of chest and skeleton)
- 3 Movable metastases

While these criteria may satisfy the technical requirements for radical mastectomy, the clinical results leave much to be desired

This discrepancy between technical operability and clinical curability was very forcibly demonstrated in an excellent series of papers by Haagensen and Stout^{1, 2, 3} Following a very critical review of the cases of breast carcinoma seen at the Presbyterian Hospital in New York, they came to the conclusion that the clinical results did not justify the procedure of radical mastectomy in many cases in which the operation was technically possible They further concluded that the "categorically inoperable" cases could be readily identified by certain definite signs of the advancement of the disease They accordingly drew up the following rule for judging the operability of breast carcinoma

Women of all age groups, who are in good enough general condition to run the risk of major surgery should be treated by radical mastectomy, except as follows

- 1 When the carcinoma is one which developed during pregnancy or lactation
- 2 When extensive edema of the skin over the breast is present
- 3 When satellite nodules are present in the skin over the breast
- 4 When intercostal or parasternal tumor nodules are present
- 5 When there is edema of the arm
- 6 When proved supraclavicular metastases are present
- 7 When the carcinoma is the inflammatory type

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- 8 When distant metastases are demonstrated
- 9 When any two, or more, of the following signs of locally advanced carcinoma are present
 - a Ulceration of the skin
 - b Edema of the skin of limited extent (less than one-third of the skin over the breast involved)
 - c Fixation of the tumor to the chest wall
 - d Axillary lymph nodes measuring 2.5 cm or more in transverse diameter and proved to contain metastases by biopsy
 - e Fixation of axillary lymph nodes to the skin or the deep structures of the axilla, and proved to contain metastases by biopsy

These investigators found 109 cases in their series which met these criteria of inoperability. Of this group, there were no permanent cures. Three cases remained clinically free of metastases for as long as five years but later died of

TABLE I—*Signs of Locally Advanced Carcinoma of Breast*

	No. of Patients
Inflammatory type of carcinoma	6
Satellite nodules	23
Pigskin appearance over one-third of the breast	35
Supraclavicular nodes	18
Edema of arm	3
Distant metastasis	5
Pregnancy and lactation	3
Lymph nodes in axilla 2.5 cm or more in transverse diameter along with some other sign of locally advanced carcinoma	19
Ulceration of skin along with some other sign of locally advanced carcinoma	37
Fixed axillary nodes with some other sign of locally advanced carcinoma	3
Fixation to chest wall with some other sign of locally advanced carcinoma	4
Pigskin appearance of less than one third of the breast with some other sign of locally advanced carcinoma	16

recurrent or metastatic carcinoma. They also presented evidence which suggested to them that if these cases, classed as categorically inoperable, were subjected to radical mastectomy, their life expectancy was shortened by about 10 months (as compared with similar untreated cases).

It was our purpose to apply these same criteria of inoperability to a group of cases of breast carcinoma (female) from the Barnard Free Skin and Cancer Hospital. We therefore reviewed all cases of carcinoma of the breast seen from 1933 to 1943, inclusive. We found 167 cases which fell into the categorically inoperable group. Of these, 100 were treated by the routine radical mastectomy or some similar radical operative procedure, and the remaining 67 were treated only by roentgen-ray.

In Table I we have classified these 100 operative cases according to the category of inoperability into which they fell.

It is obvious from Table I that many of these patients were categorically inoperable because of two or more signs of advanced carcinoma.

In Table II we have listed the various forms of therapy used in these cases. All consisted of some form of mastectomy.

Of the 100 cases which had one of the radical operative procedures as shown in Table II, only two were well and clinically free of carcinoma at the

end of five years, one for 8 years, and the other for 14 years. Both of these survivals were those in the category of a carcinoma of the breast associated with pregnancy or lactation. Inasmuch as our series contained a total of but three cases in this category, we consider these two survivals rather important, and therefore include the following brief clinical records of each.

CASE HISTORIES

M B, Hospital No 78734. A 40-year-old white female, who had had 12 previous pregnancies, three of which terminated in spontaneous abortions, was first seen in the Barnard Hospital dispensary November 20, 1939. At that time she was diagnosed clinically as having carcinoma of the left breast, with axillary metastasis. She was advised to enter the hospital for radical mastectomy. This she refused, and in February, 1940,

TABLE II—*Type of Treatment*

	No. of Patients
1 Radical mastectomy with knife	34
2 Radical mastectomy with knife plus routine postoperative roentgenotherapy	10
3 Radical mastectomy with knife plus irradiation when signs of recurrence appear	21
4 Simple mastectomy with knife plus routine postoperative roentgenotherapy	5
5 Preoperative roentgenotherapy plus radical mastectomy with knife plus roentgen treatment when signs of recurrence appear	3
6 Preoperative roentgen ray plus radical mastectomy plus routine postoperative roentgenotherapy	5
7 Preoperative roentgenotherapy plus simple mastectomy plus routine postoperative roentgen treatment	1
8 Preoperative roentgenotherapy plus radical mastectomy	6
9 Simple mastectomy with actual cautery	1
10 Radical mastectomy plus routine postoperative roentgenotherapy including roentgen castration	1
11 Shoulder-girdle amputation	1
12 Radical mastectomy with actual cautery	4
13 Radical mastectomy with knife plus roentgen castration	1
14 Simple mastectomy plus axillary-gland dissection (pectoral muscles left intact)	1
15 Radical mastectomy with actual cautery plus routine postoperative roentgenotherapy	1
16 Radical mastectomy with actual cautery plus roentgenotherapy when signs of recurrence appear	3
17 Preoperative roentgenotherapy plus radical mastectomy including supraclavicular dissection	1
18 Radical mastectomy with knife plus supraclavicular dissection	1

became pregnant. In May, 1940, she had a spontaneous abortion. In October, 1940, she was admitted to the hospital and had a left radical mastectomy—11 months after the original diagnosis. The pathologic diagnosis was adenocarcinoma of the left breast, with axillary lymph-node metastasis. She was last seen on October 26, 1948, at which time she showed no signs of local recurrence or metastasis of the carcinoma.

A N, Hospital No 57664. A 37-year-old white female, who had had 14 previous pregnancies, two of which terminated in spontaneous abortions, and one in a stillbirth. She was first seen in the Barnard Hospital dispensary April 18, 1934. Her baby was two months old and she had developed a lump in her right breast two months before the baby was born. Seven weeks before the patient came to the dispensary the baby was weaned. On May 15, 1934, three months after the birth of her child, she had a right radical mastectomy. The pathologic diagnosis was adenocarcinoma of the right breast, with axillary lymph-node metastasis. Eighteen months after the operation, she gave birth to another full-term child. She was last seen April 6, 1948, at which time there were no signs of local recurrence or metastasis of the breast carcinoma.

The question of whether or not patients with categorically inoperable carcinoma of the breast actually have their lives shortened by radical mastectomy is an important one. Haagensen and Stout believe that the life expectancy is materially shortened in the majority of instances. This is based on their figures comparing the length of life of the categorically inoperable cases who had radical mastectomy with a group of untreated carcinomas of the breast. The survival time is figured from the onset of symptoms to the time of death.

In Table III we have compared the total duration of the disease in our two groups of cases with those of Haagensen and Stout. Also included are figures from various groups of untreated cases.⁴

TABLE III—*Mean Total Duration of Breast Carcinoma—Onset to Death—in Various Groups of Cases*

A	Wyand	273	untreated cases	39 6	mean duration in months
	Lazarus-Barlow	243	untreated cases	39 8	mean duration in months
	Daland	100	untreated cases	40 5	mean duration in months
	Beatson	61	untreated cases	36 5	mean duration in months
	Powell White	59	untreated cases	32 1	mean duration in months
	Leeds	26	untreated cases	32 46	mean duration in months
	Carter-Braine	15	untreated cases	30 2	mean duration in months
	Total	777	untreated cases	38 55	Average
B	118 Presbyterian Hospital cases regarded as inoperable and denied surgery and irradiation				42 3 months
C	104 Presbyterian Hospital cases regarded as operable and treated by radical mastectomy but now classified as inoperable according to Haagensen-Stout criteria				32 3 months
D	100 Barnard Free Skin and Cancer Hospital cases regarded as inoperable by the Haagensen-Stout criteria who had the type of treatment shown in Table II				36 3 months
E	67 Barnard Free Skin and Cancer Hospital cases regarded as inoperable by the Haagensen-Stout criteria who had roentgenotherapy alone				34 2 months

DISCUSSION

Throughout the years, thousands of cases of carcinoma of the breast have been reported. These cases have at times been grouped according to rather elastic classifications as to the anatomic, pathologic or clinical degree of the disease. We feel that Haagensen and Stout have described definite signs of the advancement of carcinoma of the breast so conclusively that any worker in this field could use their classification with considerable accuracy. The various series of statistics in breast malignancy would certainly be more comparable if they were grouped according to these standards.

The question of whether or not a category of inoperability, in technically operable cases, is justifiable, is of extreme importance. The fact that we had only two possible cures in our series certainly indicates the poor results which can be expected from patients falling into this category. Strangely enough, both of these survivals were in cases associated with pregnancy. Harrington⁵ reports more encouraging results in the treatment of cancer of the breast in the course of pregnancy or lactation. Haagensen⁶ also recently pointed out that "it may be that our (Haagensen and Stout) group of cases was a particularly

unfortunate one, and that radical mastectomy is justified in these patients, provided, of course, that the disease is locally operable."

The 36.3 months average survival of our operated cases is quite close to that of 32.3 months of these reported from the Presbyterian Hospital. The Barnard cases treated by roentgen-ray alone had an average survival of 34.2 months. This is somewhat shorter than the Presbyterian Hospital cases, which were denied surgery and radiation (42.3 months).

Thus we may say that, as a rule, cases of breast malignancy which fall into the Haagensen-Stout category of inoperability will not profit by radical surgery. At this time cases of breast cancer occurring during pregnancy or lactation may be an exception to the rule. It is also possible that other criteria of inoperability may be proved to be questionable. However, only by classifying cases against definite standards of involvement will it be possible to arrive ultimately at certain standards of the most beneficial treatment.

SUMMARY

1 The survival rates of 167 cases of carcinoma of the breast categorically inoperable according to the classification of Haagensen and Stout, have been studied.

2 Of the 100 cases which were treated primarily by some form of mastectomy, only two were alive and well after five years. Both of these cases were of cancer of the breast associated with pregnancy. The average survival time of these 100 cases was 36.3 months.

3 Only groups of cases reported according to standardized anatomic, clinical and pathologic signs of advancement of the disease have any real value.

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EXTERIORIZATION OF THE CANINE VESICAL TRIGONE FOR EXPERIMENTS ON THE KIDNEY*

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INTRODUCTION

IT HAS BEEN NECESSARY to exteriorize the vesical trigone for comparison of clearances by the denervated, transplanted kidney with the intact control in trained unanesthetized dogs (Maluf, 1943) During the past year we have exteriorized, successfully, the trigones of over 20 dogs and the technic has been standardized

Exteriorization of the trigone may be essential to the success of certain experiments

1 It permits collection of urine from each ureter of unanesthetized animals Catheterization of the ureters of unanesthetized dogs by cystoscopy is difficult if not, at times, impossible In the male dog this is impossible with extant equipment When a ureter is catheterized, even once, urine is apt to trickle around the ureteral catheter and thus vitiate quantitative collection Furthermore, ureteral catheterization may evoke reflex vascular changes in the kidney and is likely to introduce infection

2 The test kidney can be simultaneously compared with the control as standard One may observe the effects of drugs on a denervated kidney as compared with the control, or may study the results of surgical procedures or various stimuli on one kidney as compared with the control (Maluf, 1949a)

3 One can actually see immediate changes in urinary flow such as may occur under conditions which result in anuria or its relief, for example, in shock, during recovery from shock, during intravenous hemoglobin infusions in states of dehydration or shock and during infusions from other intravenous drips

4 Urine can be collected quantitatively during short intervals, such as five minutes

MATERIAL

Only female dogs were used Males would necessitate total resection of the penis and thus complicate the procedure Short-haired dogs were preferred because the urine would not be as likely to excoriate, as with long-haired animals

PROCEDURE

Anesthesia was by intravenous sodium pentobarbital (from 30 to 32 mg/Kg) The skin of the groins, the inner thighs, the suprapubic region, and the lower half of the abdomen is shaved without abrasion so as to reduce

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subsequent cutaneous complications from urine. Cleansing is done gently with acetone and then aqueous zephiran, 1:1,000. Asepsis is preserved.

The ureters, bladder and most of the urethra of the dog are intraperitoneal organs (Fig 3). The meso-ureter fuses with the meso-uterus and mesovagina

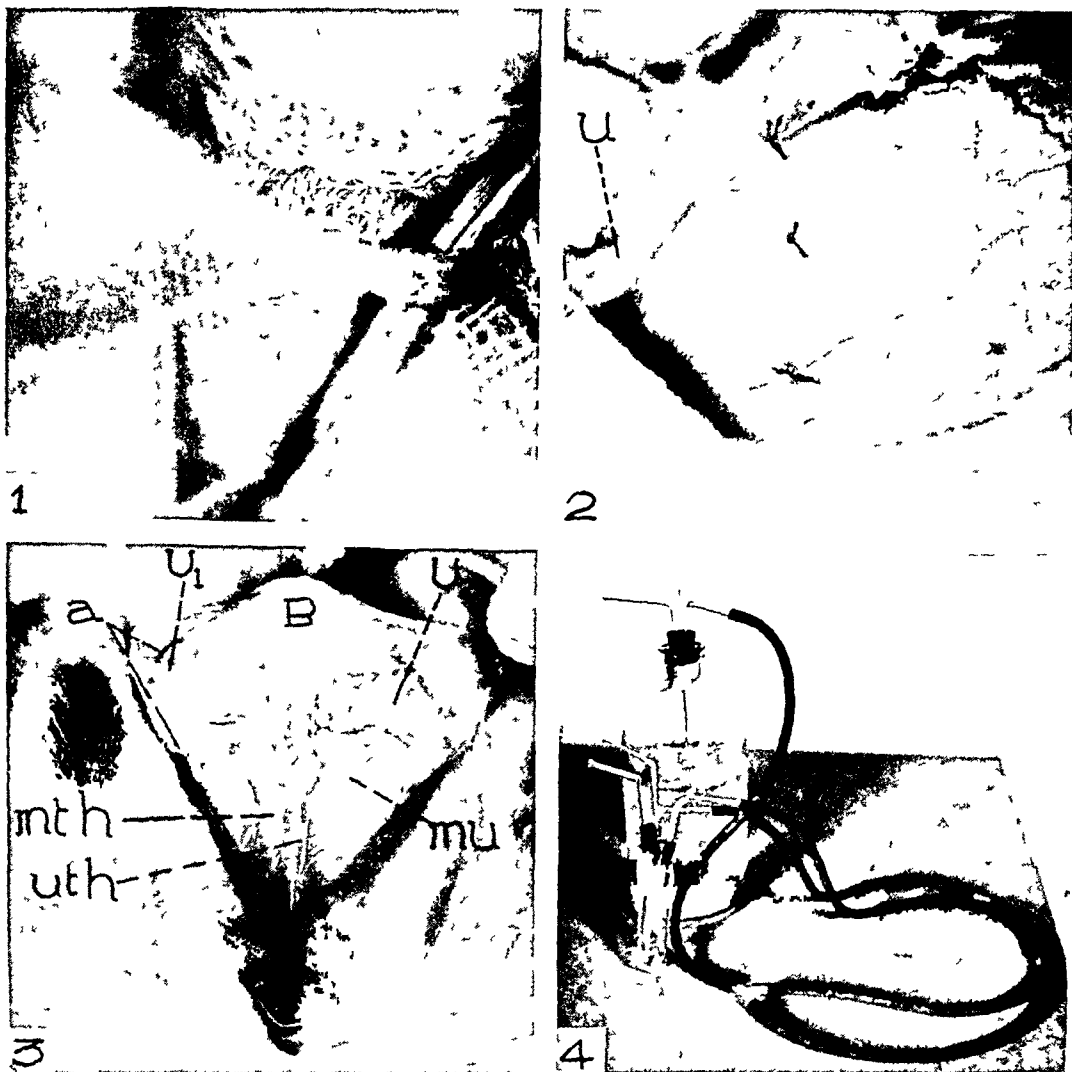


FIG 1—The intra-abdominal portion of the urethra fully mobilized prior to its ligation and division at the caudal end. The caudal end is at the right.

FIG 2—Bladder partly distended and reflected caudad (toward the right of the picture), showing the right ureter, *u*, entering the bladder (at the left of the picture) and fine ligatures applied to the longitudinal blood vessels about 2 cm from the entrance of the ureters.

FIG 3—Lower urinary tract of a female dog exposed to advantage. *B*, bladder, *U*₁ and *U*₂, ureters, *uth*, urethra, *mu*, meso-ureter, *mth*, meso-urethra, *a*, arteries to the bladder.

FIG 4—Equipment for collection of urine. Suction is applied in the direction of the arrow.

dorsally. The meso-urethra arises bilaterally from each dorsolateral margin of the urethra and is continuous with the meso-ureter. The arteries to the bladder, which are branches of the inferior mesenteric artery and of the

internal pudendal branch of the hypogastric, pass to the bladder in the meso-ureter (Fig 3)

The median longitudinal abdominal incision, from 8 to 10 cm long, extends caudad to the pubic symphysis. The bladder, usually partially distended with urine, is delivered through the wound. The practically bloodless urachus, which joins the ventral median surface of the bladder to the umbilicus and to the midline of the ventral abdominal wall caudal to the umbilicus, is divided. The ureters are identified and the membrane with free border, which extends between ureter and bladder (Fig 1) and which carries a vesical branch of the hypogastric artery, is divided between clamps close to the



FIGS 5, 6 and 7—The exteriorized vesical trigone with the adjacent central portion of the bladder and the urethra in three dogs

FIG 8—Collection of urine from the external ureteral orifices of an unanesthetized dog

bladder, and hemostatic ligatures are applied. The urethra is identified and freed with a curved dissecting scissors from its laterodorsal mesentery on each side and from adjacent fatty tissue, it is mobilized as far distally as possible (Fig 1) and ligated with 2-0 silk at its distal end.

A hemostatic clamp is applied to the urethra immediately proximal to the ligature and the urethra is divided between clamp and ligature. Care is taken to preserve the branches of the inferior mesenteric and internal pudendal arteries which enter the trigone between ureter and urethra on each side. These vessels, however, may not be essential to the viability of the trigone and the adjacent urethra. Thus, in one animal, all vessels were divided which enter

the bladder, its trigone, and the transected urethra so that the explanted trigone, the adjacent central portion of the bladder and the urethra were attached to the animal solely by the ureters. The trigone and urethra nevertheless remained pink and healthy although supplied exclusively by intramural ureteral vessels.

With a fine-curved intestinal needle, ligatures of 4-0 silk are applied to the vessels which run longitudinally on the surface of the bladder at about 2 cm from the entrance of the ureters into the bladder (Fig 1). The abdomen is closed about the mobilized exteriorized bladder without strangulating it or obstructing the urethra. In closing, sutures are not applied to the peritoneum, as they are useless caudal to the semilunar line.

The rectus abdominis muscle is approximated by sutures and the strong anterior rectus sheath is united by closely set ligatures of 3-0 silk, the subcutaneous tissues are apposed by 4-0 silk. The skin is not closed as yet.

Two Allis clamps are applied to the apex of the vesical fundus and the fundus is punctured with a knife between the clamps. The urine is allowed to flow over a towel until the bladder is empty, the towel is then discarded. With a cutting cautery, the bladder is cut through its thickness along the line of the urachus and downward so as to slit the urethra longitudinally along its ventral surface. The clamp on the distal end of the urethra is removed and cautery applied to this end of the urethra to prevent bleeding. The bladder is then trimmed off a few millimeters distal to the line circumscribed by the row of fine ligatures (Fig 2).

A narrow crescentic strip of skin is trimmed from each margin of the cutaneous incision. The bladder and the mobilized urethra are sewn to the skin by everting mattress sutures alternating with simple sutures, both of 4-0 silk. The ureteral orifices are examined for emission of urine. If the bladder is cyanotic and no urine appears from the ureters, a suture or two should be removed from the rectus sheath to relieve obstruction. The final result is an explantation of the central portion of the bladder, including the trigone and proximal portion of the urethra, to the skin of the ventral abdominal wall. The explant is covered with sterile gauze and dressed with a dry, sterile towel. The dressing is removed after 24 hours. The stitches are removed on the sixth day. Samples of the finished products appear in Figures 5, 6, and 7.

The skin of the inner thighs and the lower abdomen was treated with 70 volumes per cent ethyl alcohol once or twice daily. This tended to prevent cutaneous necrosis and sloughing due to urine. Animals which frequently licked their explant did best in the long run. If a cutaneous cicatrix developed about the exteriorized bladder, thus inverting it, the scar was cut painlessly with a knife.

COLLECTION OF URINE

The urine from each ureter was collected by suction into a 50 cc round-bottomed centrifuge tube by the equipment shown in Figure 4. This amount

of suction causes inappreciable evaporation of urine from the collecting tubes during diuretic flows. During antidiuretic flows, evaporation is appreciable during collections of 15 or more minutes. The values for renal clearance are not altered by evaporation, however, because, when the volume of urine is reduced by evaporation, the concentration of solutes rises proportionately so that the product of the concentration and the volume remain constant.

The ends of the glass tubing which were applied to the ureteral orifices (Fig. 8) were flared out into conical cups by a torch flame and a cone-shaped piece of carbon.

When catheters, whistle-tip or Braasch-bulb, were inserted into the ureters, urine trickled around the catheter and thus collection could not be complete. This, and the risk of retrograde pyelonephritis, caused abandonment of the method.

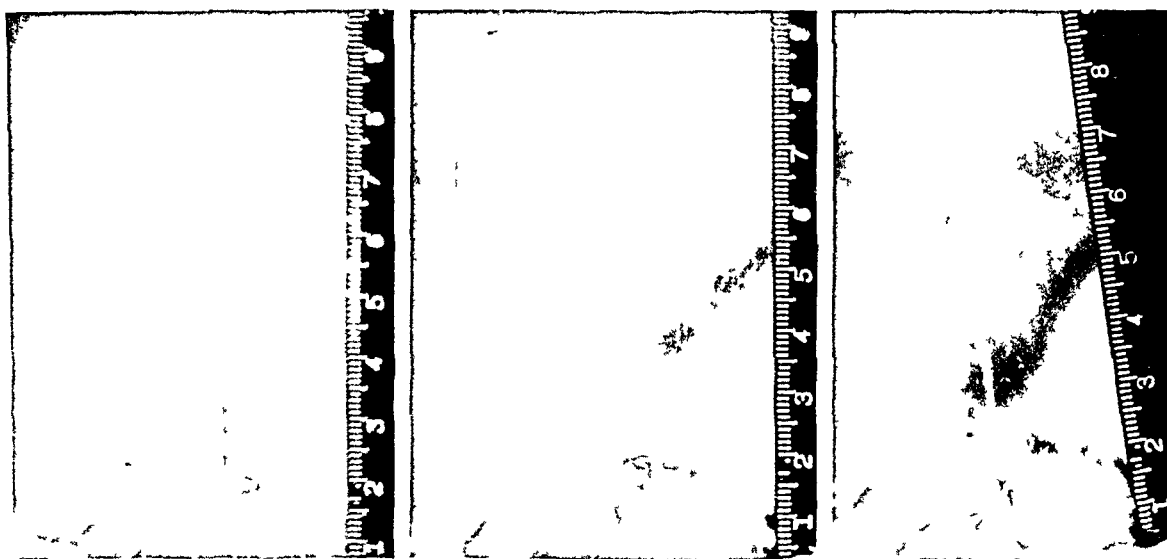


FIG. 9—Urine spurting from the external orifices during marked diuresis

The distance between the external ureteral orifices varied considerably and in an unpredictable manner for a given size of mongrel. In animals varying between 8 and 19 Kg the orifices were from 3 to 14 mm apart.

DISCUSSION

Renal function in dogs with an exteriorized trigone was measured at intervals for a few months after exteriorization. Pyelonephritis, as indicated by a reduction in effective renal blood-flow, glomerular filtration, and maximal tubular activity developed only in a minority and this probably due to neglect in daily attention to the explant and only irregular forcing of fluids by stomach-tube.

Within 60 to 90 minutes after administration of 50 cc water per Kg by stomach-tube the urine usually spurted from the ureters as a fountain-display (Fig. 9). The spurts from each ureter typically alternated, even when the volume-flow from both kidneys was significantly unequal. The

spurts, however, were not absolutely regular in time or alternation, thus making central control appear unlikely

BILATERAL CUTANEOUS URETEROSTOMY

Bilateral cutaneous ureterostomy was performed in three animals. The ureters were divided close to the bladder and mobilized for several centimeters. There is an adequate intra-ureteral arterial supply, from the renal and ovarian or spermatic arteries, which assures normal motility in spite of distal mobilization. Spurting vessels at the divided end of the ureter were carefully ligated with fine 4-0 silk. The ureters were brought out through ventrolateral stab wounds, without torsion and under optimal stretch, they were stitched to the skin by 4-0 silk, which was passed through only the ureteral adventitia by a fine-curved intestinal needle. Nevertheless, the exteriorized portions of the ureters tended to become edematous and scarred within a few days and thus to obstruct the normal outflow of urine. In man this is obviated by maintaining a catheter in the ureter until healing is complete, in the dog this was not feasible. This method of collecting urine separately from each kidney was therefore abandoned.

SUMMARY

A method of exteriorizing the canine vesical trigone, with adjacent bladder and urethra, and the manner of collecting urine from each external ureteral orifice are described.

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FACTORS INDUCING RENAL SHUT-DOWN FROM LYSED ERYTHROCYTES AN EXPERIMENTAL STUDY¹

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I INTRODUCTION

PATIENTS TO WHOM TRANSFUSIONS of blood are given are usually in shock. In acute cases, the arterial pressure is often subnormal and the cardiac output typically diminished. The renal blood flow, in shock, does not remain a constant fraction of the cardiac output but falls actually more than the cardiac output. This is true not only in shock from hemorrhage (Cournand, *et al*,¹², Lauson, *et al*,²⁷) and chronic blood loss (Bradley and Bradley⁸) but also when the cardiac output is subnormal in spite of hypervolemia, as may occur in myocardial failure (Merrill³⁴, Mokotoff, *et al*³⁵).

Individuals with chronic severe anemia may have a normal arterial pressure, an actually elevated cardiac output, an elevated venous pressure, but a remarkably low blood volume (Sharpey-Schafer⁴⁰, McMichael²⁹). Cardiac output, then, is maintained by the rise in venous pressure probably caused by a generalized constriction of capillaries and venules including renal vessels. In short, patients for whom blood transfusion is indicated have a contracted renal vascular bed and a diminished rate of glomerular filtration. A decreased effective renal blood flow in the absence of intrinsic renal damage is probably our most sensitive index of shock, especially of "chronic shock."

Intravenous administration of moderate amounts of hemoglobin or of lysed homologous or autologous red cells to normal man (O'Shaughnessy, *et al*³⁶) and normal dog may not be as nocuous as is generally believed. This suggests that patients who have undergone renal failure from a pint or less of incompatible blood probably had initial renal ischemia from a diminished blood volume.

Thus we set out to find factors which promote renal shut-down from lysed red cells and to locate the mechanism of the shut-down.

II METHODS

1 *Externalization of the vesical trigone* and collection of urine has been described in the preceding paper (Maluf³⁰).

2 *Renal Denervation* The kidney was delivered through a subcostal incision. The perinephric tissue was dissected away until the kidney was attached to the body solely by its artery, vein and ureter. The renal artery and vein were carefully freed from their adventitia, by a fine watchmaker's forceps, for a distance of about 1.5 cm. from the hilum. The ureter was freed from connective tissue for a like distance. The stripped vessels and ureter

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were painted with 50 per cent phenol in ethanol. As soon as the phenol tar-nished the vessels it was washed off with alcohol and aqueous zephiran.

To find whether the above method produces effective denervation, one kidney was so treated and the other left intact. A few days later renal clear-ances were measured simultaneously from each kidney before and after a large intravenous dose of epinephrine hydrochloride (0.22 mg/Kg). There resulted a marked reduction of effective renal blood flow and glomerular filtration in the denervated but not in the normal kidney (for details see Maluf, 1949³¹). This potentiation to epinephrine has been described by Schneider and Wildbolz⁴¹ and Kubicek and others²³. Thanks to the exterior-ized vesical trigone it was possible, in our work, to use the normal kidney as control for the contralateral denervated organ in the unanesthetized animal.

3 *Renal Function* (a) *Maximal concentration and dilution* Water was withdrawn from the cage at about 6 P.M. Next morning the antidiuretic urine was collected in one scoop after it had collected in the groin of the supine animal, hence there could be no increase in concentration by application of prolonged suction. Diuresis was produced by the administration of 50 cc tepid tap water per Kg by stomach tube. The specific gravity was measured pykno-metrically in a small thin-walled pipette with pointed tip and internal constric-tion so as to contain from 0.3 to 1.0 cc of liquid.

(b) *Glomerular filtration, effective renal blood flow and tubular maximum for para-aminohippurate* have been measured as described elsewhere (Maluf, 1949b³¹). All measurements were made on unanesthetized trained animals.

4 *Lysed Erythrocytes* Blood was collected aseptically from the femoral artery, which was exposed and painted with formalin to kill organisms which may have entered with the cutaneous incision (Pope *et al*,³⁸). The erythro-cytes were allowed to sediment in a refrigerator, if they did not sedimen ade-quately they were centrifuged. The blood was used within a few days of collection. Within half an hour before infusion, the plasma was aspirated and the cells lysed by adding one and one-half times their volume of apyrogenic distilled water. The hemolysate was transferred through a gauze filter to an Upjohn transfusion bottle containing sodium chloride for isoton-icity. The drip was at about 12 cc per minute into an external jugular vein. If the dog became too dyspneic after about 600 cc had entered, it was allowed up for a few minutes and then the infusion was completed. At the end of the infusion the hemolysate showed only a trace of methemoglobin spectrophoto-metrically. Since free hemoglobin in solution steadily changes into methemo-globin (Amberson, *et al*²), the hemolysate was used immediately. Cultures of the hemolysate on blood agar and in enriched broth showed no growth.

5 *Histamine shock* lasting over one and one-half hours was produced by subcutaneous injection of histamine dihydrochloride suspended in cottonseed oil and lanolin (Hueper and Ichniowski²²).

6 *Intra-aortic Injection with India Ink* Higgins' India ink was diluted 1:1 with 1.8 per cent sodium chloride. Under nembutal (30 mg/Kg), a

midline laparotomy was performed carefully and almost bloodlessly. Twenty cc of the diluted ink were injected in retrograde fashion through a bent needle into the aorta immediately caudal to the renal arteries. The renal pedicles were tightly clamped within half a minute of the injection. Care was taken to avoid pressure on the kidneys and any mobilization of the kidneys until the injection was over and the pedicles clamped. A No. 20 needle was usually used and this caused severe bleeding after its withdrawal unless the aorta was then clamped proximally. When the pedicle clamps were applied too late, as occurred occasionally in the earlier trials on normal dogs, the cortex sometimes stained less than the medulla. This was presumably due to a washing away of ink by the inflow of unstained blood into the cortex on its way to the medulla—a phenomenon noted by Trueta, *et al*⁴³ by roentgenography. When digital pressure was applied to a portion of the renal cortex during the injection, that local portion failed to be injected.

III RESULTS

1 Effects of Intravascularly Injected Lysed Erythrocytes on Renal Function Four normally hydrated dogs received relatively large doses of freshly lysed canine erythrocytes in isotonic sodium chloride intravenously. The dog in the sample protocol below received about 5.8 Gm of free hemoglobin per Kg. A dog has 1.2 times as much renal mass per unit of body weight as a man; furthermore, a dog's kidney is about twice as active as a man's per unit of renal weight. Thus, relative to the magnitudes of glomerular filtration and effective renal blood flow, this would be equivalent to giving

about 169 Gm of hemoglobin to a 70-Kg man $\left(\frac{5.8 \times 70}{1.2 \times 2} = 169 \right)$ This is the amount of hemoglobin contained in about 1.4 liters of blood at 12 Gm/100 cc.

These dogs had received 50 cc of tap water by stomach tube every few days to flush their kidneys and prevent retrograde infection from their exteriorized trigone. Urinary pH during diuresis was between 5.0 and 6.0. Their diet was a mixture of horse meat and cereal. The pH at the exteriorized bladder during antidiuresis was alkaline, doubtless because of the ammonia produced by urea-splitting bacteria.

Measurements of renal function (glomerular filtration, effective renal blood flow, tubular maximum for para-aminohippurate, and maximal concentrating and diluting power of the kidneys) showed practically no change from one day to several days after the infusion.

PROTOCOL

28 July, 1947 Female mongrel, 15.6 Kg. Vesical trigone exteriorized.
18 August Measurements of antidiuretic and diuretic urinary flow and specific gravity (Fig. 1)

29 August

Renal function as follows

Glomerular filtration	= 40 cc/min (left kidney)
Glomerular filtration	= 42.6 cc/min (right kidney)
Effective renal blood flow	= 186 cc/min (left kidney)
Effective renal blood flow	= 193 cc/min (right kidney)
Tubular maximum for PAH	= 11.6 mg/min (left kidney)
Tubular maximum for PAH	= 10.1 mg/min (right kidney)
Diuretic urinary flows	= 3.34-4.28 cc/min (left kidney)
Diuretic urinary flows	= 3.14-3.70 cc/min (right kidney)
pH of urine in diuresis	= 6.0
Hematocrit	= 40.4 vol %
Blood urea	= 38 mg/100 cc

8 September

270 mg nembutal, s.c., for sedation

Minutes

1,070 cc of freshly lysed red cells in isotonic saline through external jugular vein (= 73.8 cc/Kg and 5.8 Gm Hgb/Kg) The urine was brick-red within 5 minutes after beginning the infusion. Diuresis set in.

0-75

No shivering

80-85

Rates of urinary flow

2.18 cc/minutes from left ureter

2.80 cc/minutes from right ureter

90-94

Rates of urinary flow

2.2 cc/minutes from left ureter

2.9 cc/minutes from right ureter

No casts in urine

94

Vomits food eaten 3 hours before infusion (The dogs which were not fed on the day of infusion and which received red cells lysed by apyrogenic distilled water did not vomit or retch on the same day after the infusion, see protocols below)

95

Walks to cage in good condition

135

Vomits more of food eaten before the infusion. Drinks water

345

Retches occasionally. Active and alert. Red stream of urine from cage to gutter about 3 meters away, still urinating amply. Water removed from cage. Has drunk 500 cc water in 165 minutes.

Feces normal in color and consistency, sclerae normal in color

No further vomiting

Next Morning

About 260 cc dark-red, thick urine in pan below cage. Hemochromogen still prominent in urine. Holds 800 cc tap water given by stomach tube to evoke diuresis.

Renal function as follows

Glomerular filtration	= 37.6 cc/min (left kidney)
Glomerular filtration	= 42.4 cc/min (right kidney)
Effective renal blood flow	= 208 cc/min (left kidney)
Effective renal blood flow	= 222 cc/min (right kidney)
Tubular maximum for PAH	= 12 mg/min (left kidney)
Tubular maximum for PAH	= 14.1 mg/min (right kidney)
Diuretic urinary flows	= 1.61-2.1 cc/min (left kidney)
Diuretic urinary flows	= 1.7-2.5 cc/min (right kidney)
pH of diuretic urine	= 6 to 6.5
No casts in urine	

RENAL SHUT-DOWN FROM LYSED ERYTHROCYTES

13 Sept

No water since evening before in preparation for concentration and dilution tests

Sp Gr = 1.004 to 1.047 (left kidney)

Sp Gr = 1.002 to 1.053 (right kidney)

Can concentrate and dilute as before the infusion (also Fig 1)

21 Sept

Both kidneys again show normal concentrating and diluting power
Dog remains healthy

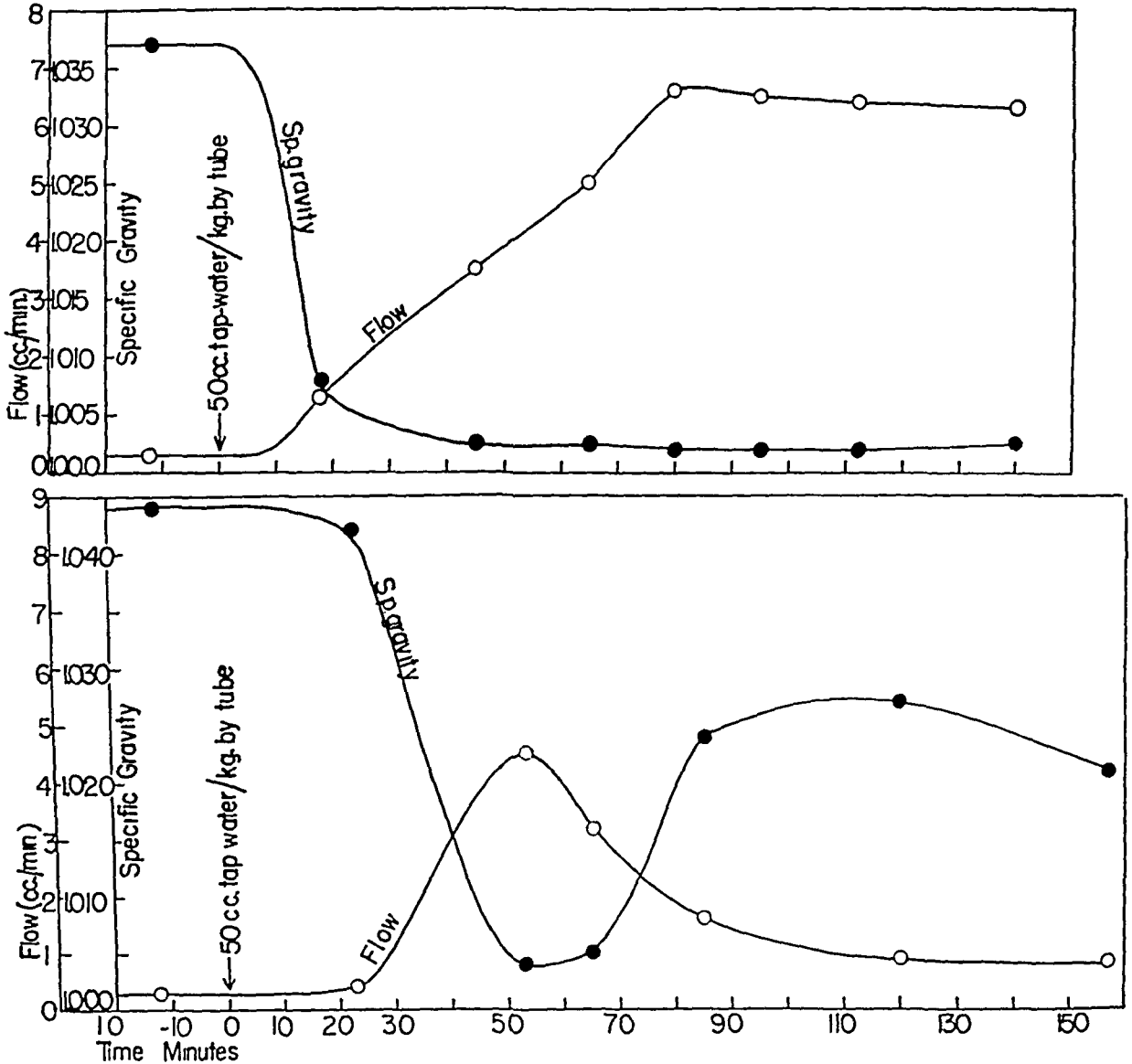


FIG 1—Diuretic and antidiuretic urinary flows and specific gravities before and after ingestion of a large quantity of water in a normally hydrated dog before (upper graph) and one day after (lower graph) the infusion of lysed red cells. Free hemoglobin received 6 Gm./Kg. Maximal and minimal concentrating power is still present after the infusion.

2 Effects of Intravascularly Injected Lysed Erythrocytes Plus Dehydration on Renal Function There was a marked difference between the effects of intravascularly injected lysed red cells into well hydrated and into severely dehydrated dogs. The former lived without obvious renal injury. The latter became anuric or oliguric and underwent severe renal damage. Below is one

exemplary protocol out of six, all of which had a uniform outcome. To study their renal circulation in the anuric or oliguric phase, the dogs were sacrificed before a probable uremic death.

Dehydration was continued until the urinary flow was 0.006 cc/Kg/min, this being the value found by Harrison and others²⁰ to foster renal shut-down from 4 Gm of hemoglobin per Kg or from 1 Gm of methemoglobin per Kg.

Any fall in blood volume, which probably occurred during dehydration, was more than fully compensated by the intravenous injection of the hemolysate. The volume infused was about two-thirds of the theoretical normal blood volume and the external jugular veins became engorged. The arterial pressure was always normal, as indicated by the prominently visible femoral pulse. Consequently, the postinfusion renal shut-down could not have been due to hypopnea.

One dog underwent *renal denervation* about two weeks before receiving the infusion. This conspicuously failed to prevent renal failure.

PROTOCOL

27 Mar 48	Female mongrel, 12 Kg Vesical trigone exteriorized
12 May	Renal function as follows
	Glomerular filtration = 35.1 cc/min
	Effective renal blood flow = 226 cc/min
	Tubular maximum for PAH = 8.1 mg/min
	Diuretic urinary flow = 1.76-2.88 cc/min
	NPN = 57 mg/100 cc
	Hct = 32 vol per cent
13 May	Water out of cage in A.M., commencement of dehydration
	Weight = 11.8 Kg
16 May	Refuses food for first time
18 May	Mouth and nostrils parched, temples, cheeks and eyes sunken
A.M.	Urinary flow = 0.005 cc/Kg/min
	Weight = 10.4 Kg
	Hct = 38.9 vol per cent
	NPN = 31 mg/100 cc plasma
Early P.M.	100 mg nembutal S.C. for sedation
Minutes	
0	Infusion of lysed red cells in isotonic NaCl begun
10	Reddish-brown pigment in urine
40	Diuresis begins, about 420 cc of hemolysate in, dog dyspneic, struggles and whimpers, contralateral jugular vein is distended
	Infusion discontinued. Dog allowed about
55	Dyspnea ceases, infusion recommenced
	Mild diuresis continues with dark brown-red pigment
75	Total amount infused = 555 cc, = 53.3 cc/Kg and 2 Gm Hgb/Kg
115	Animal drowsy, sleeping in cage, external jugular veins distended, no vomiting
265	About 50 cc "black water" in pan below cage. Less drowsy, allowed 50 cc water by mouth
325	No vomiting as yet. allowed another 50 cc water by mouth
Next morning	No fluid in pan under cage, thighs quite dry
	Markedly oliguric, less than 0.004 cc urine per min, urine dark brown and turbid. Alert but weak.

11 30-40 A M	Drank 950 cc milk	
12 50 P M	Allowed 300 cc water, which was soon vomited together with some of the milk drunk two hours ago	
1 20-1 42 P M	No urine from ureteral orifices, even on dilating orifices T = 101.7°F (normal), R = 19/min External jugular veins are prominent when lying down but dog still appears strikingly dehydrated and emaciated Drowsy but readily awakened Iris tinged red	
2 00 P M	Weight = 11.3 Kg	NPN = 156 mg Hct = 39.5 vol per cent
	Hgb in plasma is almost as intense as in infusion solution	
2 10-2 20	Still anuric	
2 25 P M	Nembutal 30 mg/Kg I V for anesthesia Laparotomy (midline without blood loss) liver not enlarged, viscera grossly normal, stomach distended with about 400 cc curdled milk and some gas Gross appearance of kidney normal 20 cc of India ink, which had been diluted with an equal volume of 1.8 per cent NaCl, were injected rapidly and in retrograde fashion into the abdominal aorta somewhat caudal to the right renal artery The renal pedicle was then clamped immediately The renal cortex was as well injected as the medulla (Fig 6) The renal capsule was not under tension	

The kidney was fixed in 10 per cent formalin Frozen sections (8μ and 25μ) were immersed in water to uncurl Temporary preparations were covered with a droplet of water and a coverslip The loops of the glomerular tuft were well filled with India ink (Figs 2 and 3), which was restricted entirely to the blood vessels There were numerous eosinophilic casts filling practically every collecting tubule in the field (Fig 4) Elongate, light-brown *crystals*, probably of methemoglobin, were numerous in the tubular lumina (Fig 5) The tubules were not dilated There was intracellular pigment and, as shown by H and E mounts, no "lower nephron nephrosis"

In another dog, a 16-Kg pointer which had received 3.2 Gm of hemoglobin per Kg as lysed red cells, there was an appreciable urinary flow of 0.187 cc per minute by the second postinfusion day, this animal never having become anuric As a gauge of renal function, however, this flow would be misleading since the plasma NPN was 182 mg/100 cc, there was an almost hundred-fold reduction of glomerular filtration (98 cc per minute initially, down to 1.14 cc per minute on the second postinfusion day) and of *effective* renal blood flow (761 cc per minute initially, down to 6.4 cc per minute on the second postinfusion day), and there was a failure to concentrate urine as shown by a low specific gravity and a urine-plasma-creatinine ratio of only 6 These values contrast strikingly with the oliguria of normal kidneys, in which there is maximal concentration during severe dehydration Thus the urine-plasma-creatinine ratio of dogs subjected to comparable dehydration alone exceeds 200 (see below) Injections of India ink into the abdominal aorta during life showed that in these dehydrated postinfusion dogs, the *absolute* renal blood flow was ample and the anuria or oliguria could not be explained by renal ischemia Any hypovolemia which may have

resulted from dehydration was more than fully compensated for by the infusion. The injections were retrograde to avoid the objection that intrarenal vessels may be forced open by the small force of injection. Equal deposition of India-ink particles in blood vessels of the renal cortex and medulla showed that there was no shunting of blood from the cortex. These facts, together with the large number of pigmented and crystalline casts in the tubules and the

FIG 2

FIG 3

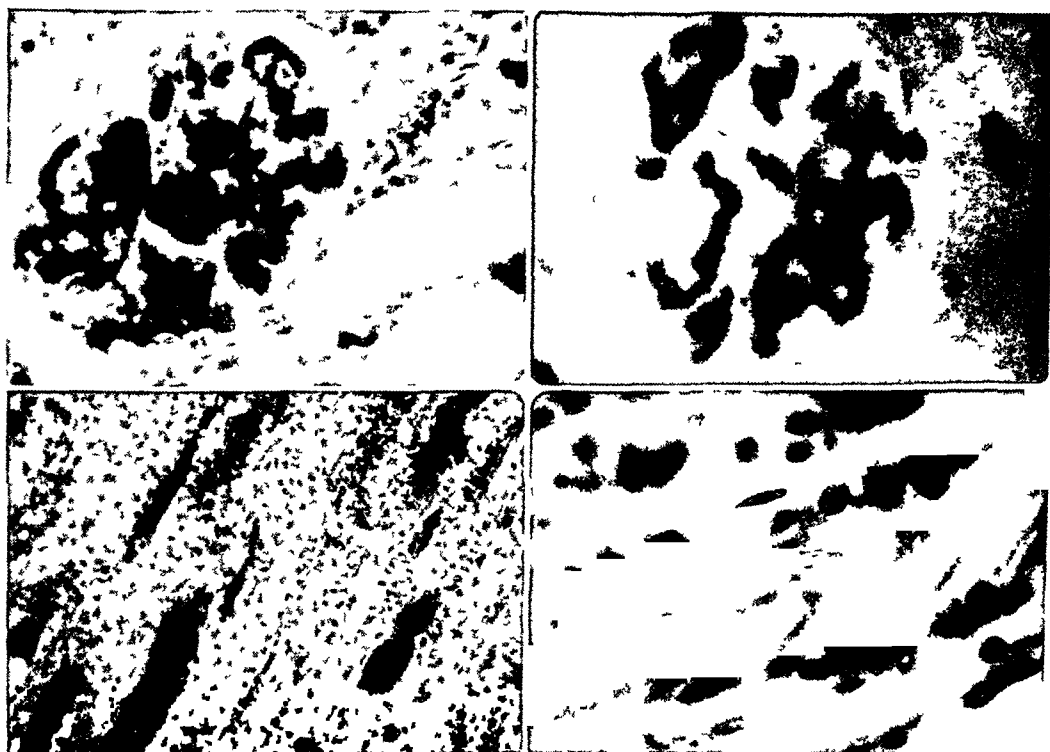


FIG 4

FIG 5

FIG 2—Glomerular tuft filled with particles of India ink injected during life into the aorta while the animal was anuric from intravenous administration of lysed erythrocytes superimposed on dehydration. Kidney fixed in formalin, section while frozen, and stained with hematoxylin and eosin.

FIG 3—Glomerular tuft containing particles of India ink, from same kidney as shown in Figure 2, fresh, frozen preparation, not stained.

FIG 4—Pigmented amorphous casts filling collecting tubules of same dog as is seen in Figure 2. Kidney fixed in formalin, sectioned while frozen, stained with hematoxylin and eosin.

FIG 5—Elongate crystals, probably of methemoglobin, in the collecting tubules of the same dog as is seen in Figure 2. Same preparation as in Figure 4.

absence of histologic evidence of renal cellular damage, indicate that the anuria or oliguria are, initially, at least, caused by tubular obstruction. The fact that the animals were not allowed to progress and die in uremia may explain the absence of increased intracapsular tension, absence of histologically obvious renal cellular damage and absence of peritubular edema.

3 Effects of Dehydration Alone on Renal Function It was essential to study the effects of dehydration alone on renal function. The following protocol

shows that severe dehydration alone actually can reduce, reversibly, glomerular filtration and effective renal blood flow by about half. The specific gravity of the urine, however, becomes high. This contrasts with the low fixed specific gravity in oliguria from intravascular administration of lysed red cells plus dehydration. Parallel with the high specific gravity is the high urine-plasma ratio for creatinine, which contrasts with a low ratio in oliguria from dehydration combined with intravascularly given lysed red cells (see protocol). The renal shut-down in the latter dogs is accurately depicted not so much by the oliguria *per se* as by the great fall in glomerular filtration and effective renal blood flow. Unilateral renal denervation in a dog, the protocol of which is not presented here, did not alter the extent of reduction in renal function by dehydration alone.

PROTOCOL

28 November, 1947 Female mongrel 9.3 Kg
Exteriorization of vesical trigone NPN = 32 mg/100 cc

28 May, 1948 Renal function as follows
Glomerular filtration = 58.9 cc/min
Effective renal blood flow = 438 cc/min
Diuretic urinary flow = 3.2-3.89 cc/min
Urine-plasma ratio for creatinine = 18.4
Hct = 49.2 vol per cent

9 June *Water out of cage, commencement of dehydration*

14 June Rejects food for first time

16 June Weight = 7.9 Kg NPN = 36 mg/100 cc
Urinary flow = 0.0061 cc/Kg/min
Sp Gr = 1.042
Renal function as follows
Glomerular filtration = 23.5 cc/min
Effective renal blood flow = 187 cc/min
Urinary flow = 0.10 cc/min
Urine-plasma ratio for creatinine = 235.0
Hct = 54.3 vol per cent
Shortly after the above measurements the dog was allowed to drink water as desired (= about 1,000 cc), a large part of which was promptly ejected. Alert and active.
No further vomiting. One and one-half hours later it ate 1 pound of canned canine food. Six hours later it ate another pound.

19 June Weight 9.2 Kg Hct = 49.2 vol per cent
Renal function as follows
Glomerular filtration rate = 45.2 cc/min
Effective renal blood flow = 270 cc/min
Diuretic urinary flow = 1.8 cc/min

4 Effect of Intravascularly Injected Lysed Erythrocytes Plus Shock on Renal Function. It was important to find whether renal shut-down would result from the injection of lysed red cells into normally hydrated dogs if shock were superimposed.

Reversible shock was produced by injecting histamine dihydrochloride in oil subcutaneously into normally hydrated dogs. The infusion of lysed red

cells was performed when the dog was in prostrate shock. Even though the volume of solution infused was almost as great as the theoretical circulating blood volume, the effect of the infusion on the shock picture was not striking. The anuria of shock changed only to a scant urinary flow during the infusion. A few hours later, even after complete recovery from shock, there was absolute anuria or marked oliguria.

The oliguria caused by intravascularly injected lysed red cells plus shock is a genuine renal shut-down with at least a hundred-fold decrease in glomerular filtration and effective renal blood flow, a low urinary specific gravity, a

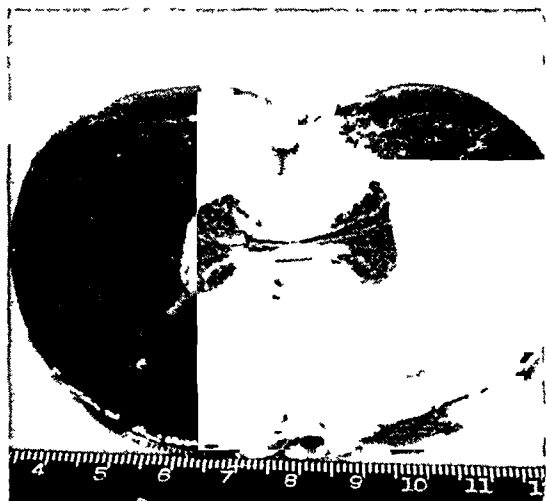


FIG 6

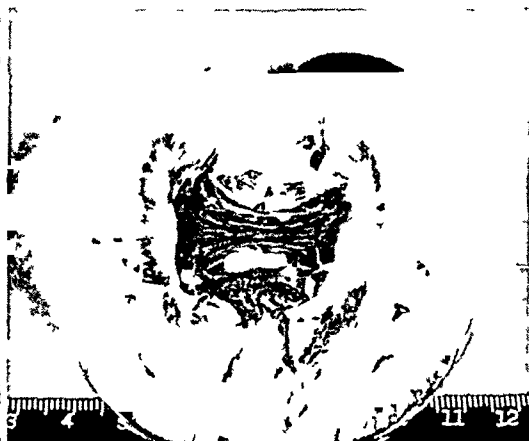


FIG 7

FIG 6—Divided kidney of the dog which was sacrificed in anuria from intravenous administration of lysed red cells superimposed on dehydration (same dog as in Figs 2 to 5). India ink was injected during life into the aorta and the renal pedicle was clamped immediately after. Both the cortex and the medulla are well injected.

FIG 7—Divided kidney of the dog which was sacrificed in anuria from intravenous administration of lysed red cells superimposed on histamine shock. The arterial pressure was normal at this time. Intra-aortic injection of India ink with immediate subsequent clamping of the renal pedicle resulted in equal and normal injection of both cortex and medulla.

low urine-plasma ratio for creatinine, and a marked uremia. This type of oliguria is identical with that from lysed red cells plus severe dehydration, and contrasts with the oliguria of severe dehydration alone (see above).

Injections with India ink, as described above, during the phase of *post-shock* renal shut-down, resulted in equal and adequate injection of the renal cortex and medulla. This indicates a normal absolute renal blood flow and shows that the renal shut-down cannot be due to a shunting of blood from the renal cortex to the medulla. The casts in the tubular lumina indicate extensive tubular obstruction as the primary cause of the shut-down. Here again the marked fall in effective renal blood flow, as measured by the para-aminohippurate clearance, is obviously due to inability of the tubules to allow passage of the hippurate because of their being obstructed.

Animals which were put into shock with the above dose of histamine, but which did not receive lysed red cells, recovered completely although they were

anuric for more than an hour India ink injections during the anuria from shock showed merely a diminished injection of the kidneys with more ink in the renal cortex than in the medulla Thus the anuria during histamine shock is the result of general renal ischemia and not the outcome of a shunting of blood from the renal cortex to the medulla

The experiment of injecting lysed red cells into normally hydrated dogs in shock was done on three animals

PROTOCOL

Female mongrel, 13 Kg Vesical trigone had been exteriorized	
6 June, 1948	Renal function as follows
	Glomerular filtration = 50 cc/min
	Effective renal blood flow = 290 cc/min
7 June	Weight = 13.0 Kg Food and water withdrawn from cage at 6 P.M.
8 June	Urinary flow = 0.16 cc/min
	Sp. Gr. of urine = 1.041
	pH of urine = 6.0
Minutes	
0	Femoral arterial pulse strikingly visible through skin, exteriorized bladder pink, R = 20/min
	70 mg histamine dihydrochloride (= 5 mg/Kg) in 3 cc cottonseed oil plus lanolin, s.c. through a No. 18 needle, tape was applied over the site
23	Lies prone
33	Stands and ejects bile-stained vomitus
58	Around and walking, defecates
68	Lying down with eyes half closed, femoral arterial pulse no longer visible but thready to palpation
77-82	Urinary output not measurable, 1 drop, bladder a mottled purple-red
	Dog markedly drowsy
	Blood draw now showed Hct = 43.7 vol per cent,
	NPN = 29 mg/100 cc
78	Infusion of lysed canine red cells in isotonic NaCl begun
78-133	No shivering, 1 to 2 drops of urine, normal in color
134	Urine appears, not a copious flow, dark brown in color
153	Infusion discontinued Volume infused = 650 cc (= 50 cc/Kg and 3.76 Gm Hgb/Kg)
158	No diuresis, urinary flow still scant, dog licks lips, drowsy, lies prone
163	Blood sample drawn now shows Hct = 41.7 vol per cent, Plasma Hgb = 2.8 Gm/100 cc
168-173	Dark-brown urine, less than 0.02 cc/min
273	Urinary flow still less than at 168-173 min
	Femoral arterial pulse still not visible but feels more forcible, dog can stand but prefers to lie down Bladder no longer markedly cyanotic
	T = 101° 6F
296	Vomits
396-404	Femoral arterial pulse now distinctly visible although not as prominent as initially
	Urinary flow less than 0.01 cc/min urine dark brown
	Iaundice apparent on exposed areas of skin such as inner portions of earflaps and belly
660	Anuric Alert and active Ate almost 1 pound canned canine food, refused the rest Allowed about 200 cc water

Next morning Urinary flow = 0.01 cc/min, urine dark brown, jaundice increased, no "black water" in pan under cage during night but about 300 cc of what looks like chiefly vomitus Dog moderately alert and active
Blood showed
NPN = 1122 mg/100 cc
Hct = 40.3 vol per cent
Plasma Hgb = 2 Gm/100 cc
Drank, as desired, 140 cc water, which was vomited after 20 minutes

Evening Is listless, retches when offered food

Second postinfusion day Listless but can walk T = 99°8F Urinary flow is less than 0.006 cc/min, urine a light brown, stools not tarry, no hyperpnea

Third postinfusion day Weight = 11.7 Kg T = 98°6F R = 48
Femoral arterial pulsations visible, alert but listless, neuromuscular hyperirritability, Chvostek Practically no fluid in pan at bottom of cage, a small, loose, deep-brown stool, urine a dark orange Bleeding time elevated
Urinary flow = 0.079 cc/min
Sp Gr of urine = 1.020, Hct = 47.3 vol per cent
NPN = 312 mg/100 cc
Plasma Hgb still appreciable (less than 1 Gm/100 cc), plasma stained with bile pigment
Renal function
Glomerular filtration = 0.40 cc/min
Effective renal blood flow = 1.28 cc/min
Urine-plasma ratio for creatinine = 5.1
Laparotomy under nembutal anesthesia Subcutaneous tissues and viscera jaundiced, gastro-intestinal tract empty, renal capsule incised in situ and found not to be under tension, extensive oozing of blood from renal cortex when this was nicked slightly Kidney excised, deeply stained with brown pigment, pigment in medulla darker than in cortex When the kidney was divided and squeezed gently, more blood seemed to ooze from the cortex than from the medulla There was thus no evidence of renal cortical ischemia Intra-aortic India ink showed equal and normal injection of cortex and medulla (Fig 7)

5 Effects of Intravascular Hemolysis by Distilled Water on Renal Function Large amounts of apyrogenic distilled water were injected rapidly intravenously into normal hydrated dogs Only mild, transient systemic effects resulted The four dogs so treated received an average of 90 cc of distilled water per Kg in 18 minutes, which, relative to renal activity (see above), is equivalent to injecting 2,600 cc into a 70-Kg man Renal function, as indicated by concentration and dilution tests and by the plasma—NPN, was not reduced Landsteiner & Finch²⁶ injected 200 cc of distilled water in from one to two minutes into patients who were not in shock and found no rise in blood urea Voris⁴⁴ gave 1,000 cc of distilled water intravenously to patients and noted no ill effects and only mild hemoglobinuria

PROTOCOL

Female mongrel, 11.6 Kg, vesical trigone had been exteriorized, normally hydrated, no food since night before Initial NPN = 54 mg/100 cc

14 March, 1948	Left renal artery and vein divided
17 March	Evaluation of renal function
	Glomerular filtration = 33.7 cc/min
	Effective renal blood flow = 174 cc/min
	Tubular maximum for para-aminohippurate = 13.5 mg/min
	Diuretic urinary flows = 1.46-2.86 cc/min
10 June	
2 20-2 38 P M	1,025 cc apyrogenic distilled water were injected through a three-way metal cock and No. 15 needle into an external jugular vein using a 20-cc syringe, i.e., 88.5 cc water/Kg in 18 min. The exteriorized trigone showed no immediate diuresis or obvious pigmentation of the urine. The dog was not manifestly uncomfortable. It lay down comfortably, shook itself occasionally and belched gas.
	Hct-before I V = 35.7 vol per cent
	Hct-after I V = 34.6 vol per cent
	Plasma hemoglobin immediately after I V = 200 mg/100 cc
3 19-3 24 P M	Marked diuresis. 4.4 cc/minute of light reddish-brown urine. Dog returned to cage in good condition. Extensive diuresis continues.
5 30 P M	Ate 1 pound canned canine food.
12 June	NPN = 41 mg/100 cc. Plasma normal in color. Dog concentrates and dilutes urine normally.

6 *Effects of Intravascular Hemolysis by Distilled Water Plus Shock on Renal Function* Human beings who are not in shock have been shown to tolerate, without renal damage, rapid intravenous injection of at least 900 cc of distilled water. It has been suggested that the renal shut-down and uremia which may follow irrigation of the bladder with tap water during transurethral operations on the prostate gland may be due to a combination of shock with intravascular hemolysis (Creevy & Webb,⁴ Landsteiner and Finch,²⁶ McLaughlin, and others²⁸). It has not been possible, however, to produce renal failure in dogs by a combination of shock plus injection of distilled water even in quantities which one might not venture in man.

The dog of the following protocol had only one kidney, underwent 90 minutes of absolute anuria from severe shock lasting two hours, was rapidly infused with 95 cc/Kg of distilled water during the anuria, and did not recover from anuria until 70 minutes after the infusion. This combination of apparently near-maximal adverse circumstances nevertheless failed to produce renal failure. Similar results occurred in the two other dogs so tested. It is possible that overhydration and reversible shock without blood loss prevented uremia. Creevy (1947) has pointed out that aggravating factors in man may be renal vasoconstriction from rapid blood loss, arteriosclerosis and pyelonephritis. This deserves further investigation.

PROTOCOL

	Female mongrel, weight = 8.85 Kg, vesical trigone had been exteriorized
7 May	Right nephrectomy
18 May	Renal function as follows
	Glomerular filtration = 48.9 cc/min

Effective renal blood flow = 250 cc/min

Tubular maximum for para-aminohippurate = 17.2 mg/min

No food or water since evening before

18 June

Minutes

0 Femoral arterial pulse visible through skin, exteriorized bladder pink,
R = 22 min5 mg histamine dihydrochloride per Kg in cottonseed oil and lanolin,
s.c. over chest

7 Dog lies prone and licks lips

12 Gets up and defecates

22 Again lies prone

42 Retches

63 R = 40/min Femoral arterial pulse no longer visible and faint to
palpation, exteriorized bladder cyanotic

63 to 70 Anuric

74 to 90 850 cc apyrogenic dist water I.V., i.e., 95 cc/Kg in 16 minutes
Vomits once during procedure Defecates

Still anuric

93 Uncomfortable, abdomen distended and rather tympanitic, grunts,
stands voluntarily but unsteadily95 Blood drawn now shows NPN = 31 mg/100 cc Hct = 40.3 vol
per cent, Plasma Hgb = 300 mg/100 cc

Dog stands but with head lowered

125 Dog still anuric, lying down

160 Urinary flow sets in, brownish-red urine, dog has had about 90 min-
utes of absolute anuria Femoral pulse now forcible to palpation but
still not visible through skin, dog lying down, no diuresis as yet520 Only 300 cc of brownish fluid in pan at bottom of cage, urine a light
reddish-brown, is distinctly lighter than six hours ago Dog obviously
recovered from shock but refuses food or waterNext morning Weight = 8.2 Kg 750 cc dark brown liquid in pan at bottom of cage
Urine is light reddish-brown

Hct = 44.2 vol per cent

NPN = 39 mg/100 cc

Urinary flow = 0.55 cc/min

Plasma hemoglobin somewhat below yesterday Eats ¼ pound of
canned canine foodSecond postinfu- Urine straw-colored and output copious, appetite normal Food and
sion day water out of cage at 5 P.M. for concentration and dilution test
tomorrowThird postinfu- Weight = 7.8 Kg, Hct = 47 vol per cent, NPN = 31 mg/100 cc
sion day Sp. Gr. of concentrated urine (at 0.16 cc/min) = 1.029

Sp. Gr. of dilute urine (at 2.4 cc/min) = 1.004

IV DISCUSSION

We have shown that normally hydrated dogs may withstand intravenous injection of lysed canine red cells which, so far as relative degrees of renal activity are considered, would be equivalent to the infusion of more than a liter of incompatible blood into a 70-Kg man. This tolerance is true in spite of aciduria. Earlier studies which indicated a greater tolerance to hemoglobinemia in alkalinuria (Baker and Dodds,³ for rabbits, De Gowin *et al.*,¹⁵ for dogs) were inadequately controlled especially as to dehydration. Thus, De

Gowin and others made their dogs acidotic by mixing 8 Gm of ammonium chloride with one-half pound of beef per day. The dogs occasionally refused this food "for several days at a time." Furthermore, while 7 of the 28 dogs died of renal failure, 6 died of intercurrent infection. As for rabbits, Yorke and Nauss⁴⁶ have noted the importance of dehydration in posthemoglobinemic anuria. Anuria and death occurred in the rabbits fed dry diets but not in those eating green food. They postulated a low glomerular filtration pressure due to dehydration. De Navasquez¹⁶ and Yuile and others⁴⁷ failed to reproduce the results of Baker and Dodds in rabbits. Flink¹⁷ injected from four to six Gm of hemoglobin per Kg into dogs and found just as severe renal damage in dogs with alkalimuria as in those with aciduria. When the initial concentration of hemoglobin in the plasma exceeded 3.7 Gm/100 cc, renal insufficiency always developed. He found no difference between the effects of solutions of hemoglobin crystals and of lysed red cells. Bing^{6, 7} found from 0.5 to 1 Gm of hemoglobin per Kg practically innocuous to dogs, whether in aciduria or alkalimuria, and that methemoglobin was relatively nocuous in aciduric but not in alkalimuric dogs. Bing's anuric dogs, however, may have been dehydrated as a result of large ammonium chloride feedings. Furthermore, ammonium chloride itself, even in doses considerably smaller than Bing's, is somewhat nephrotoxic to man (Markert¹²), and especially to rabbits (Govan and Paikes¹⁹). Webster and others (1935) have pointed out that in the presence of physiologic salt concentrations, the state of aggregation of hemoglobin is not influenced by pH.

O'Shaughnessy and others³⁶ injected intravenously into a patient with cancer 50 Gm of human hemoglobin in 30 minutes. This is equivalent, at least in terms of hemoglobin, to over 300 cc of incompatible blood. No obvious renal damage resulted. Gilligan and others¹⁸ and Ottenberg and Fox³⁷ obtained similar results with smaller quantities of hemoglobin, however. Gilligan and others noted chills, fever and severe abdominal pains in the patient receiving the largest quantity of stroma-free human hemoglobin, 16.4 Gm, *i.e.*, only 0.25 Gm per Kg.

The importance of dehydration in causing renal shut-down from homologous hemoglobin has been shown by Yorke and Nauss⁴⁶ and Lalich^{24, 25} for rabbits and by Harrison and others²⁰ for dogs. The present work in part confirms their findings. We have further found that severe dehydration will reduce the effective renal blood flow and rate of glomerular filtration in the dog. This may be true in man as is indicated by the falling urea clearance and the rising NPN in man's blood during progressive dehydration (Adolph and others¹).

That shock plus hemoglobinemia or myoglobinemia can result in renal failure has been shown by Corcoran and Page¹⁰ (1945). The present study in part confirms this.

The cause of renal shut-down from hemoglobinemia has been hypothesized on the basis of renal vasoconstriction, mechanical tubular blockage or

renal tubular damage Evidence for renal vasoconstriction by free hemoglobin in the blood stream was produced by Reid³⁹ and Mason and Mann³³ Hesse and Filatov²¹ (1933) found a fall in arterial pressure and renal volume upon infusion of lysed autologous blood into dogs Subsequent workers, who have performed the infusions aseptically, have not been able to confirm these findings (Bing,⁷ 1944, Flink,¹⁷ 1945, Corcoran and Page,¹¹ 1947) The diuresis which directly follows an infusion of hemoglobin solution into a normal dog and which tends to occur even in a dehydrated or hypopiesic dog contraindicates vasoconstriction as a primary factor in the renal shut-down

Our studies with India ink indicate no obvious decrease in *absolute* renal blood flow during the anuria or oliguria which follows infusion of lysed red cells superimposed on reversible shock or dehydration Our measurements of the renal clearance of para-aminohippurate, however, show a very marked fall in *effective* renal blood flow These findings imply that damaged or obstructed tubules fail to extract the hippurate from the blood circulating through the renal parenchyma It is significant that these were postinfusion studies and that the animals had recovered completely from shock or had their blood volume fully replenished from any loss incurred during dehydration They nevertheless had marked renal shut-down These India-ink studies also show that this renal failure cannot be ascribed to a shunting of blood from the renal cortex to the medulla Such a shunt has been described by Trueta and others^{42, 43} in a certain percentage of rabbits upon stimulation of the sciatic nerve or after injection of staphylococcal toxin

Renal failure occurred when intravascular injection of lysed red cells was combined with dehydration or shock even in kidneys which had been denervated

Corcoran and Page⁹ incidentally noted that dogs in hemorrhagic shock with denervated kidneys responded to blood transfusion by a disproportionately slow and incomplete return toward normal of renal clearances They therefore suggested that spinal anesthesia may actually interfere with the recovery of renal circulation in shock treated by transfusion

Our dogs were sacrificed after a postinfusion period of from two to three days, when they were quite uremic At this stage, the renal capsule was not under tension and there was no histologically obvious renal cellular damage Many of the tubules in a field were occluded by brown casts or crystals The casts were best preserved by fixing the kidney in 10 per cent formalin shortly after the animals were sacrificed and sectioned while frozen a few days later Most of the casts were lost when the kidneys were sectioned while frozen without prior fixation The loss probably occurred when the frozen sections were immersed in water to unroll Although there was considerable loss of casts in specimens carried through paraffin in Flink's¹⁷ studies, the majority of tubules were occluded by casts in dogs with serious or fatal renal damage This has been confirmed by Lalich²⁴ and Harrison and others²⁰ Harrison and others teased out casts by microdissection and found that they dissolved rapidly in buffers below pH 5.2 and above pH 7.6 and that they had the

spectral properties of methemoglobin. The studies of several investigators including Bell,⁷ indicate that tubular obstruction by pigmented casts is a prominent feature in the renal shut-down of the "transfusion-kidney." By showing the nontenability of the postulate that lysed red cells produce renal cortical ischemia, by studying the kidneys histologically within the first two days after infusion, and by showing that dehydration and shock are predisposing factors, we are left, as our apparent sole gross explanation, the following: *The mechanism of renal failure from the intravascular introduction of a moderate quantity of lysed red cells is primarily due to tubular obstruction from casts of hemochromogen combined with a low rate of glomerular filtration.*

V SUMMARY

1 As much as 5.8 Gm per Kg of free homologous hemoglobin, as lysed red cells, may be given intravenously to a normal, well-hydrated dog without producing any striking sign of renal damage. In terms of lysed red cells and relative to the degree of renal activity, this is equivalent to giving at least one liter of incompatible blood to a 70-Kg man. The initial urinary pH of the dogs was from 5.5 to 6.0.

2 When a dog is dehydrated until its urinary flow is only 0.006 cc/Kg/min, intravenous infusion of from 2 to 3 Gm per Kg of free hemoglobin as lysed red cells will lead to immediate anuria or oliguria and then severe uremia. The resultant oliguria is not of a concentrated but of a dilute urine. A nearly normal urinary output may mask a severe renal shut-down, as indicated by a hundred-fold decrease in the rate of glomerular filtration and *effective* renal blood flow.

3 The oliguria of severe dehydration alone, on the other hand, is of a urine with high specific gravity. Severe dehydration of the above extent results in an approximate halving of glomerular filtration and *effective* renal blood flow. This is reversible on rehydration and the animal promptly recovers.

4 Denervation of a kidney several days prior to dehydration does not influence the changes mentioned in 2 and 3.

5 Intravenous injection of from 3 to 4 Gm per Kg of free hemoglobin as lysed red cells into a dog in profound reversible shock and anuria from histamine will lead to postshock anuria or oliguria and then to severe uremia. As in the combination of dehydration with intravascular injection of lysed red cells, there results an immense fall in glomerular filtration and *effective* renal blood flow and a low urine-plasma ratio for creatinine.

6 Intra-aortic India-ink injections during life show that there is normal intraglomerular and peritubular circulation during the anuria or oliguria of the renal shut-down which follows intravenous injection of lysed red cells during dehydration or shock. There is no shunting of renal blood flow from the renal cortex. The tubules are filled with pigmented amorphous and crystalline casts.

7 The renal capsule is not under tension and there is no histologic evidence of renal cellular damage during the first two or three days of uremia

8 A dog can stand rapid intravenous injection of 100 cc of distilled water per Kg without striking reduction in renal function and with complete recovery Relative to the degree of renal activity, this is equivalent to rapid injection of 26 liters into a 70-Kg man

9 A dog can stand rapid intravenous injection of at least 95 cc of distilled water per Kg, even during profound histamine-shock with its resulting anuria, without undergoing marked reduction in renal function and with complete recovery

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THE EFFECTS OF ULTRAVIOLET RADIATION ON THE EXPOSED BRAIN—EXPERIMENTAL STUDY*

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THE USE of ultraviolet radiation in the operating room was introduced by Hart¹ in 1936, thereby adding another effective measure for the control of postoperative wound infection. Hart and his associates^{2, 8} demonstrated in subsequent publications that air-borne pathogenic organisms were responsible for the majority of infections in clean operative cases and that such organisms could be largely eliminated by ultraviolet radiation. Experimental studies to determine the effect upon wound healing of this physical agent, as well as those concerned with its bactericidal effects, were carried out by this group before recommending its use in the operating room.

A brief account of the reaction of the brain to ultraviolet radiation was given by Hart and Sanger⁷ and additional unpublished data derived from animal studies have permitted its use in our neurosurgical operative rooms during the past ten years. In this publication we shall describe the pathological alterations which occur in the cerebral cortex upon exposure to ultraviolet radiation as compared to those which occur upon exposure to atmospheric air alone.

METHOD

Twenty-five dogs were used during the experiment and all operations were carried out under aseptic technic. Intraperitoneal anesthesia was employed using nembutal one grain per five pounds of body weight. An incision was made in the scalp and the temporal muscle was reflected laterally. A small trephine opening was then placed in the skull and the opening enlarged with rongeurs to a diameter of approximately 3 cms by 2.5 cms. The dura was opened in an elliptical fashion and reflected laterally, exposing an area of the cortex 2.5 cms by 2 cms. Twelve of the dogs were exposed to ultraviolet radiation (at an intensity of 16 microwatts per square centimeter)‡ for various intervals from 15 minutes to 3 hours. In a second group of 12 dogs the brain was exposed to air for the same periods of time. One animal was anesthetized for three hours as a control experiment and sacrificed on the

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† We are indebted to the Lamp Division of the Westinghouse Electric Manufacturing Company for supplying the irradiation units used in this study. Dr D G Sharp is responsible for arranging this unit and measuring the intensities used.

‡ This intensity was selected due to the fact that it was the same as the present reading in the neurosurgical operation room.

seventh post-anesthetic day, without exposure of the cortex to air or ultraviolet radiation. During the entire exposure of the cortex to air or ultraviolet radiation and air, it was kept moist with Ringer's solution. The dura was closed with interrupted black silk. The muscles and scalp were sutured with interrupted black silk and a sterile gauze collodion dressing applied. The animals were sacrificed by bleeding while under nembutal anesthesia on the third, seventh and twenty-eighth day. The carotid arteries were injected with 10 per cent formaldehyde. Blocks were taken through the exposed area and from the opposite hemisphere and fixed in 10 per cent formaldehyde U S P and ammonium bromide solution of formaldehyde. Sections were stained with hematoxylin phloxine, toluidine blue, gold chloride and silver carbonate.

RESULTS

The changes which were observed were progressively dependent upon the length of time of the exposure. After exposure to ultraviolet radiation for 10 minutes the meningeal vessels began to dilate and gradually the brain became congested. Changes in the meningeal vessels in the group exposed to air alone were not apparent until approximately 45 minutes after the exposure had commenced and were never as prominent as those exposed to ultraviolet radiation. Swelling of the brain as noted by bulging of the exposed area was present in the 2-hour and 3-hour radiation groups but was never sufficient to prevent closure of the dura. The swelling was not noted in the one-half or one-hour exposure to ultraviolet radiation. None of the exposures to air, except the 3-hour ones, produced any degree of bulging of the cortex.

Microscopic sections from the specimens exposed to air for 15 or 30 minutes (Fig 1) or to ultraviolet radiation for 15 minutes showed very little change. The first definite changes which were detected were in those animals exposed to ultraviolet radiation for 30 minutes (Fig 2). These animals revealed slight thickening of the arachnoid with dilatation of the meningeal vessels and a moderate number of red and white blood cells in the subarachnoid space. There was dilatation of the subpial vessels and widening of the perivascular spaces of the gray matter. These changes became more pronounced in the 1-hour (Fig 4), 1½-hour, 2-hour and 3-hour specimens (Fig 5), with white blood cells becoming rather numerous in the subarachnoid space in the exposures of one hour. Subpial hemorrhages were present in the 3-hour exposures to ultraviolet radiation with small perivascular hemorrhages (diapedesis) throughout the gray matter. In one of these animals there was fairly extensive destruction of a triangular area of the cortex by hemorrhage. The brains that were exposed to air for one hour (Fig 3) or longer showed red blood cells in the subarachnoid space, slight thickening of the arachnoid and an increase in the size of the perivascular spaces but the changes were only slight as compared to those exposed to ultraviolet radiation. In none exposed to air were hemorrhages noted.

The neurons after exposure to ultraviolet radiation for 30 minutes (Fig 6) began to show definite changes, mainly shrinkage and acute swelling which



Figs 1-4 — (Legends on opposite page)

became more marked as the exposure time was prolonged. The neurons which showed shrinkage were located for the most part in the superficial layers of the cortex. These cells were deeply stained, shrunken and triangular. The nucleus and nucleolus could be recognized as such except in the longer exposures when the cell body was markedly shrunken and the nucleus and

nucleolus could not be identified. The perineuronal space about these cells was widened. The cells which revealed acute swelling or chromatolysis were more prominent than those which showed shrinkage, and were confined to the deeper layers of the cortex. The cytoplasm of these cells contained vacuoles, and the nucleus was enlarged and displaced to one side of the cell, or occupied the entire cell body. In some instances the contour of the cell was lost, as though the cell membrane had ruptured and all that remained was the

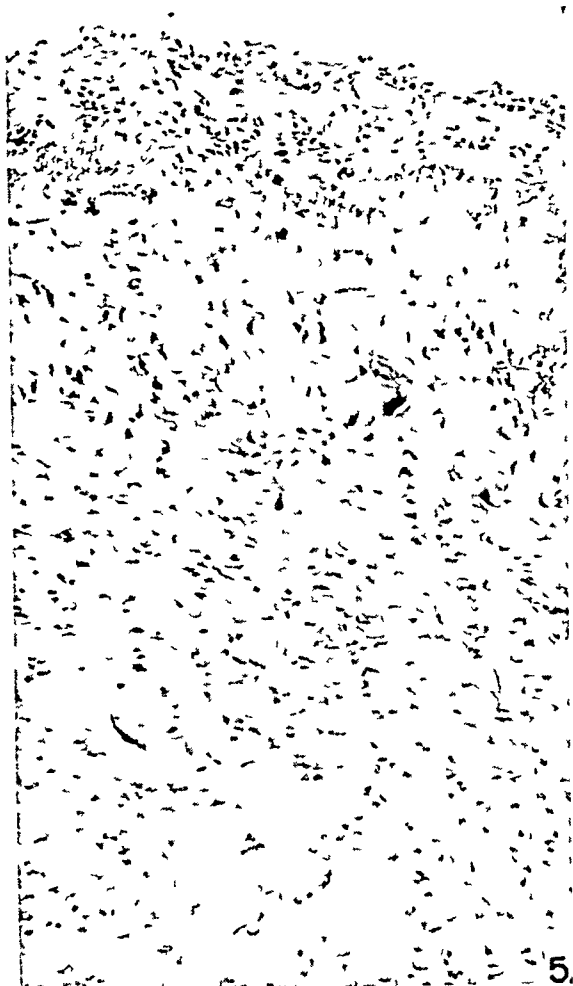


FIG 5—Exposure to ultraviolet radiation 3 hours, sacrificed on the seventh day (Hematoxylin phloxine 110x)

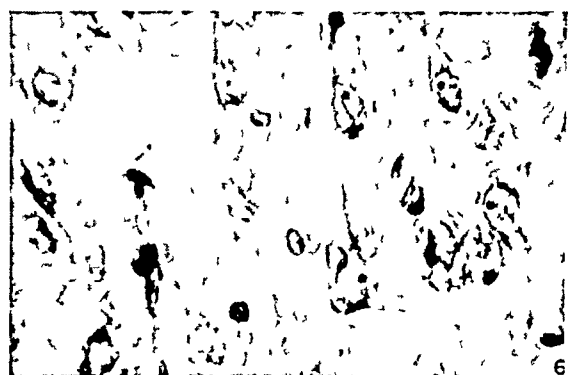


FIG 6—Exposure to ultraviolet radiation 30 minutes, sacrificed on the seventh day (Toluidine blue 580x)

swollen nucleolus, fragments of the cell outline or a clear space. These neuronal changes were very pronounced in the 3-hour exposures to ultraviolet radiation and the gray matter presented a honeycombed appearance with a loss of the normal lamination. Minor changes of the same type were present in the exposures to air and such changes began to appear at approximately one hour

FIG 1—Exposure to air for 30 minutes, sacrificed on the seventh day (Hematoxylin phloxine 120x)

FIG 2—Exposure to ultraviolet radiation 30 minutes, sacrificed on the seventh day (Hematoxylin phloxine 120x)

FIG 3—Exposure to air 1 hour, sacrificed on the seventh day (Hematoxylin phloxine 120x)

FIG 4—Exposure to ultraviolet radiation 1 hour, sacrificed on the seventh day (Hematoxylin phloxine 120x)

The astrocytes became increased in size and number. This hyperplasia of the astrocytes first occurred in the 30 minute (Fig 8) exposure to ultraviolet radiation and progressed with the time of the exposure. This change first occurred in the marginal layer but progressed to involve the gray and white matter in the longer exposures. The brain of the dogs exposed to air for 1½ hours began to show a hyperplasia of the astrocytes in the marginal layer.

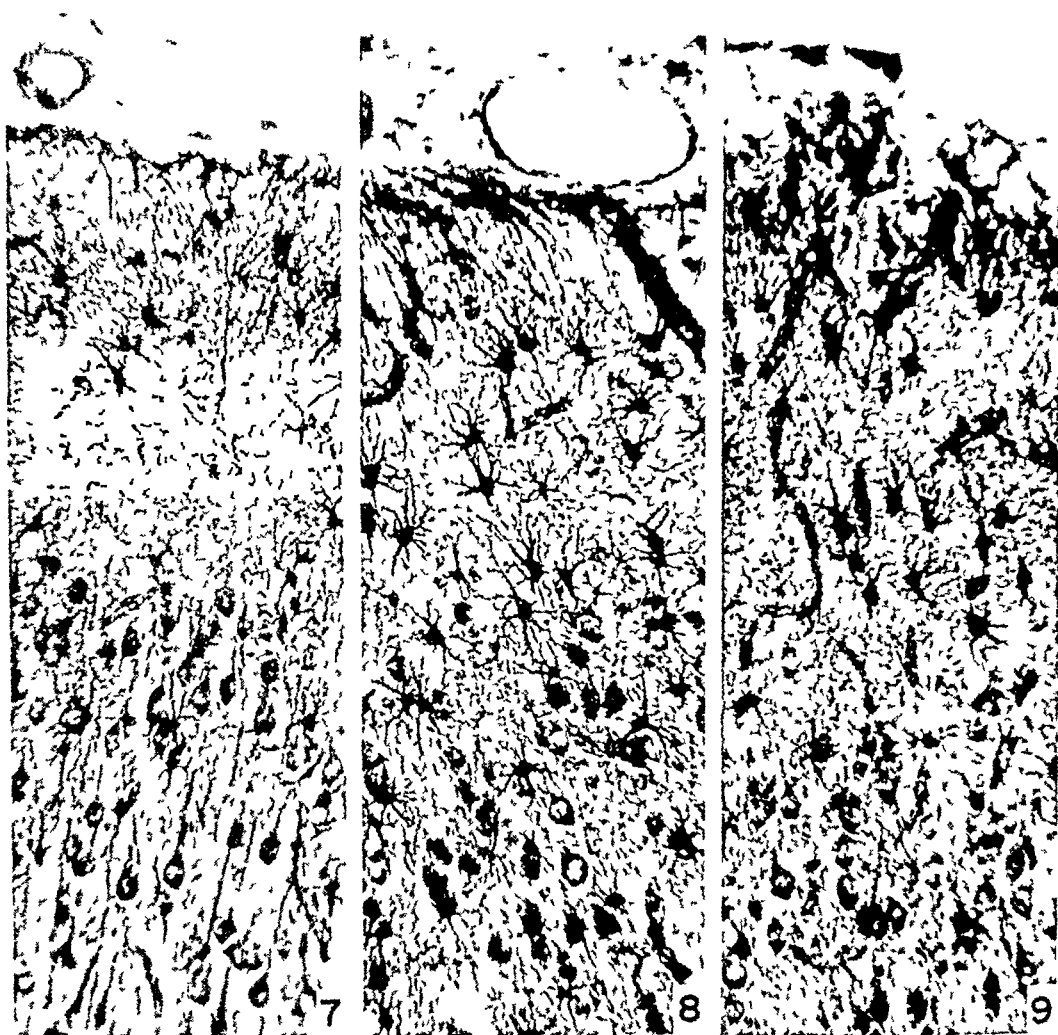


FIG 7—Exposure to air for 30 minutes, sacrificed on the seventh day (Gold chloride 680 λ)

FIG 8—Exposure to ultraviolet radiation 30 minutes, sacrificed on the seventh day (Gold chloride 680 λ)

FIG 9—Exposure to ultraviolet radiation 1 hour, sacrificed on the seventh day (Gold chloride 680 λ)

In none of the exposures to ultraviolet radiation or air were there changes in the oligodendroglia.

In the animals which were exposed to ultraviolet radiation for 30 minutes and sacrificed at the end of 28 days (Fig 10) there was a marked regression of the changes noted at the end of seven days. In these specimens there was a

slight thickening of the arachnoid but no cells were present in the subarachnoid space. The neurons (Fig 11) had practically assumed their normal form except for a few shrunken cells still present in the superficial layers of the cortex. There remained a slight patchy decrease in the number of neurons, with occasional neuronaphagia. There was also still noted a slight increase in the astrocytes in the marginal layers.

The control animal which was anesthetized for three hours and not exposed to air or ultraviolet radiation failed to show any microscopic changes.

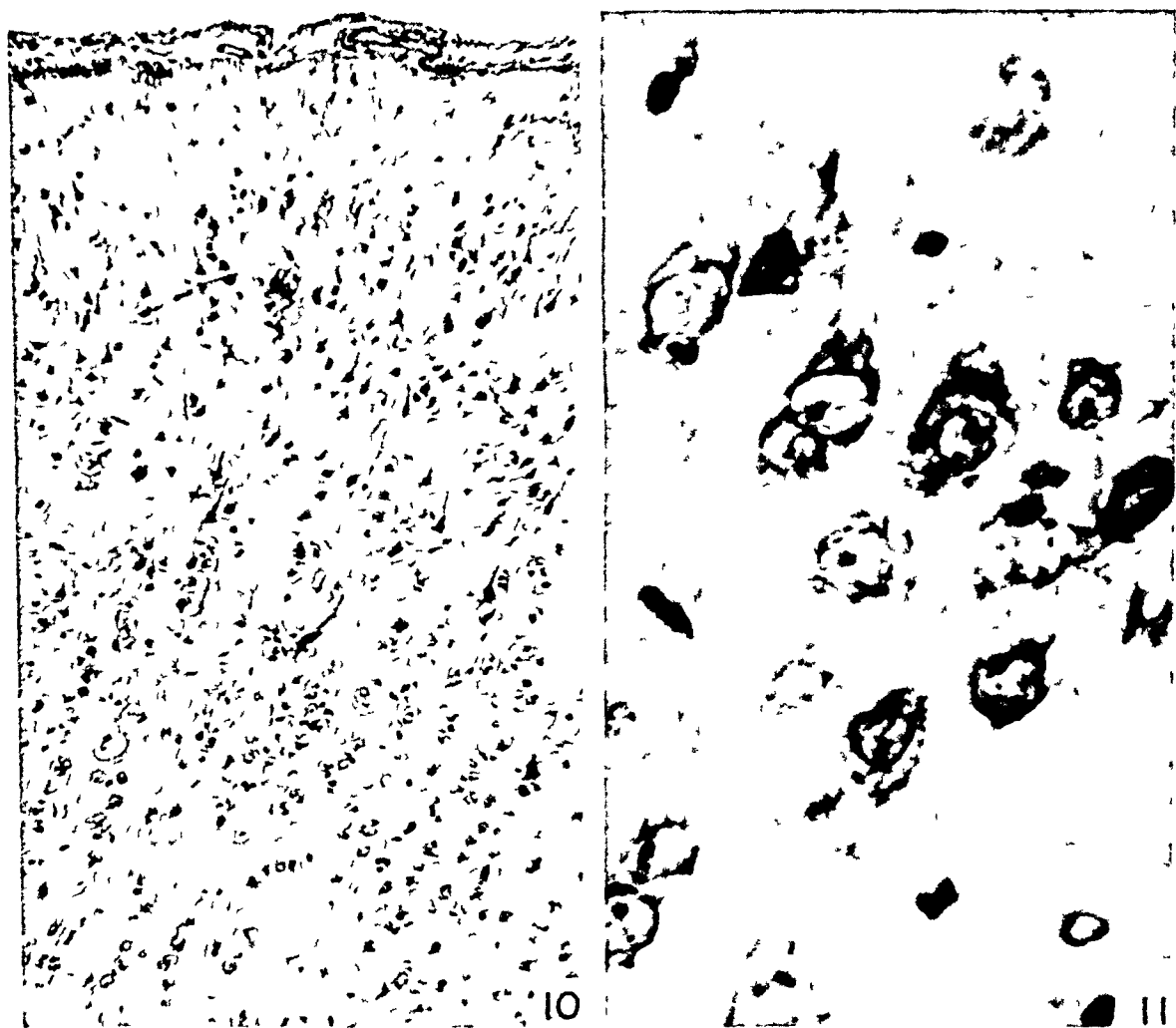


FIG 10—Exposure to ultraviolet radiation 30 minutes, sacrificed the twenty-eighth day (Hematoxylin-phloxine 125 \times)

FIG 11—Exposure to ultraviolet radiation 1 hour, sacrificed the twenty-eighth day (Toluidine blue 660 \times)

COMMENT

Prados, Strowger and Fendel⁹ reported in detail the reaction of the brain to air exposure. Our control animals verified their findings although the exposure time was shorter. The changes produced by ultraviolet radiation are similar to those which occur with air exposure but they occur much sooner.

It is our opinion that there is no contraindication to the use of ultraviolet radiation in the operating room if the usual neurosurgical technique of pro-

tecting the exposed and uninvolved cortex is followed. The changes which do occur with a 30-minute exposure are regressive and this time interval should be sufficient to inspect the cortex and remove a lesion if the uninvolved cortex is kept covered with moist cottonoid strips. This statement is also borne out by the fact that from a clinical standpoint we have never observed a postoperative reaction which we could attribute to the ultraviolet radiation. From our experiments one must however warn against its use when it is necessary to keep the brain exposed for long periods of time while stimulating the cortex to locate an epileptic focus or in the course of obtaining electroencephalograms from the cortex.

We have not had the opportunity to study its effects upon the human brain except in three cases of topectomies. In these cases the area to be resected on one side was exposed to ultraviolet radiation for 45 minutes immediately before removal. There were no cellular changes noted in these cases. No case had presented itself in which we have felt justified in exposing the cortex and waiting several days before doing the resection.

SUMMARY

The effects of ultraviolet radiation upon the exposed cortex first appear in approximately 30 minutes and become more pronounced as the length of time is increased. These changes consist of a meningeal reaction with thickening of the arachnoid, the appearance of red and white blood cells in the subarachnoid space, a dilatation of blood vessels, an increase in the size of the perivascular and perineuronal spaces, the shrinkage and chromatolysis of the neurons and an increase in the size and number of the astrocytes. These changes were also noted in the brains of the animals which were exposed to air alone but they were not as marked and took a longer exposure time before they appeared. The changes in both instances become regressive if not carried beyond a certain exposure period of approximately 30 minutes.

We feel that no contraindication exists to the use of ultraviolet radiation in the neurosurgical operating room if the uninvolved cortex is protected with the same meticulous care that is mandatory in all modern neurosurgical procedures.

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DISARTICULATION OF AN INNOMINATE BONE
(HEMIPELVECTOMY)

FOR
PRIMARY AND METASTATIC CANCER*†

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INTRODUCTION

The radical resection of an innominate bone, its contiguous soft tissues and the subjacent lower extremity as a means of ablating cancer, has received recently renewed interest ^{1, 2, 3, 4, 5, 6}

The decreasing mortality rate attendant upon the performance of this procedure has removed the diffidence which previously has been associated with hemipelvectomy. Moreover, as increasing knowledge is obtained of the natural history of certain forms of cancer and as the more conservative methods of therapy are evaluated, the status of this operation in our present surgical armamentarium can be determined.

Since the first successful resection by Girard in 1895⁷ 158 resections have been recorded. The efficacy of any surgical procedure can be determined by evaluating reported mortality and survival rates.

The purpose of this presentation is to record our experience with eight patients who were subjected to radical exarticulation of the lower extremity through the sacroiliac synchondrosis.

Although the period of follow-up is still too short to permit final evaluation, certain lessons could be gleaned by the study, and though the number of cases of this series are few, they constitute, nevertheless, the largest series in the American literature to date.

Definition. Hemipelvectomy (disarticulation of innominate bone) refers to that surgical procedure in which the entire innominate bone, contiguous somatic tissues (buttock), and entire subjacent lower extremity are resected en masse. Because the cancellous nature of the innominate bone favors the wide dissemination of cancer throughout its structure, the entire bone should be

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† Published with permission of the Medical Director of Veterans Administration who assumes no responsibility for the opinions or conclusions drawn by the authors.

removed^{1, 2} Not infrequently it is necessary to resect such other viscera as peritoneum, testicle and spermatic cord structures (Case 7), intra-abdominal viscera,⁸ and periaortic lymph nodes (Case 8)

Synonyms There is little unanimity of terminology regarding this operation The procedure of radical resection of an innominate bone and lower extremity has been variously described as interiliosacropubic amputation,^{9, 10} transiliac amputation,¹¹ interinnomino-abdominal amputation,^{3, 15} intiapelvia-abdominal amputation,¹⁴ interpelvi-abdominal amputation,¹³ hindquarter resection,⁷ ilio-abdominal amputation,¹⁰ sacroiliac disarticulation, interilioabdominal amputation,^{12, 23} and hemipelvectomy^{21, 22} For the purpose of this discussion the authors prefer the term hemipelvectomy

Historical An excellent review of the historical development of the operative procedure from the first attempt by Billroth in 1891 is presented by Gordon-Taylor and Willis³ Following Billroth's experience, several unsuccessful resections were attempted, and in 1895 Girard performed the first successful resection⁷ Pingle in 1916 presented his experience with four cases¹³ In 1935 Gordon-Taylor and Willis recorded five instances where transiliac resections were performed,³ and in 1946 Gordon-Taylor and Patey presented the records of 21 personal cases (the largest series reported) and reviewed the literature to that year⁴ Morton introduced the procedure to America⁵ Sugarbaker and Ackerman (6 cases)¹ and Pack and Ehrlich (6 cases)² have presented the most recent experience with this operative procedure

INDICATIONS

Hemipelvectomy is indicated for those neoplasms which involve the hip joint, pelvic parietes, or soft tissues of the iliac region, and which cannot be surgically extirpated by more conservative methods The following tabulation classifies the various conditions where this procedure may be indicated

(1) Primary malignant neoplasms of the innominate bone such as osteogenic sarcoma, and periosteal fibrosarcoma²

(2) Primary malignant neoplasms of the femur which have invaded the hip joint (Case 6)

(3) Cancer of the soft somatic tissues of the upper thigh, inguinal region, or buttock, which have invaded the hip joint or extended through the obturator foramen to involve the pelvic parietes

(4) Metastases to the iliac region which have infiltrated the hip joint, the pelvic parietes, or which, because of local extension, have precluded extirpation of the disease by less radical procedures such as radical groin dissection, and so forth In this group are included

(a) Metastases from primary epidermoid carcinomas or sarcomas of the lower extremity (Case 8)

(b) Metastases from malignant melanoma which cannot be treated by hip joint disarticulation or radical groin dissection

(c) Metastases from carcinoma of the penis (Case 2) or rectum in certain selected cases

(d) Metastases from certain distant primary tumors, as kidney carcinoma (Case 7) or thyroid carcinoma⁵

In all instances where the resection is performed for the treatment of metastases, the primary neoplasm must be controlled or controllable

(5) Certain massive benign tumors of the innominate bone, as chondroma,⁶ osteochondroma,¹⁴ or of the somatic tissue of pelvic area (neurofibroma)² if they cannot be resected adequately by other less radical procedure

(6) For palliation in certain instances of generalized metastases melanoma (Case 5), Kaposi's hemorrhagic sarcoma,² spindle cell sarcoma⁴ where the lesion of the groin produces a bulky infected and painful mass, which cannot be controlled by any other modality

(7) Certain infections and trauma,^{4, 5} which will not be discussed in this presentation

In this series the resections were performed for synovial sarcoma, fibrosarcoma, periosteal fibrosarcoma, iliac metastases from a primary squamous carcinoma, Ewing tumor, and metastatic hypernephroma. One palliative resection was performed for melanosarcoma

SURGICAL PROCEDURE

Preoperative preparation The adequate control of fluid, electrolyte, and colloid balance as for any major surgical procedure and correction of anemia and other metabolic abnormalities are imperative

The patients are placed on an antibiotic regime (penicillin, 50,000 units every four hours) one week before surgery. Two days before surgery they receive streptomycin (1 Gm each day) and the day before operation, 6 Gm of sulfadiazine is administered. The evening before operation a gentle enema is given

All of the patients were males, hence we have had no experience with vaginal preparation. However, thorough cleaning of the vagina is recommended⁵

Preoperative debridement, or cautery excision of certain lesions as described by Pack and Ehrlich,² in our experience is unnecessary. In bulky fungating tumors a small drape is sutured over the lesion at the time of surgery. An indwelling urethral catheter is inserted before the patient comes to the operating room

Preoperative preparation of the psyche of all candidates for this operation is rewarded postoperatively by a grateful patient who bravely resigns himself to the deformity. None of our patients regretted their decision to submit to this surgical procedure

Anesthesia Endotracheal inhalation anesthesia (nitrous oxide, oxygen, and ether) was used in the earlier cases. Recently a combination of Baird's solution* and nitrous oxide has been found a very satisfactory anesthetic agent. The patient can be moved easily when necessary and this mixture is desirable for the hypotension which not infrequently attends the operation

* A solution of pentathol and curare containing 25 milligrams of sodium pentathol and 5 units of d-tubocurarine chloride per cubic centimeter

Technic of Operation The operative area is prepared with zephiran, the anal opening is closed with sutures, and the scrotum is fastened to the opposite thigh with a few silk sutures

The patient is placed on the table in a tilted position with his involved side supported on a kidney rest. The involved extremity is slightly flexed at the hip and knee, and is externally rotated and abducted.

Incision The incision extends from the symphysis pubis, parallel to the inguinal ligament, to a point two centimeters superior to the anterior superior iliac spine. Through this incision the entire anterior dissection is accomplished

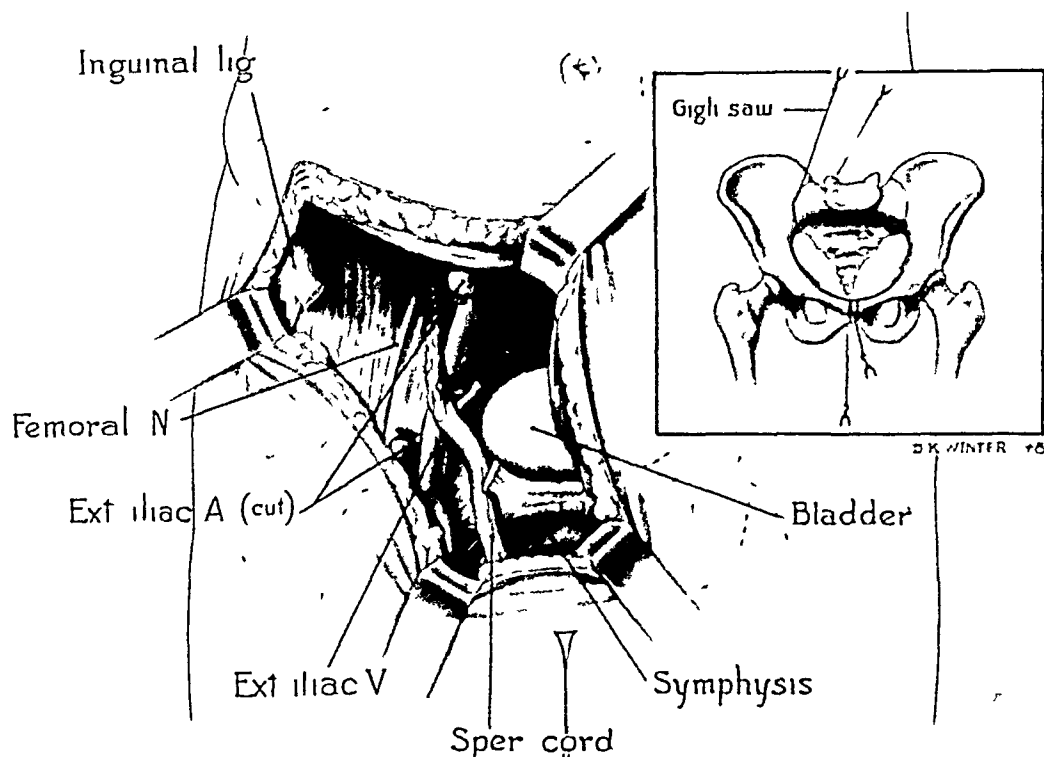


FIG 1 — *Anterior Dissection* The incision which extends from the symphysis pubis to 2 cm superior to the anterior superior spine of the ilium has been deepened. The inguinal ligament severed at its attachments and the external iliac artery ligated and clamped. After retracting the spermatic cord structures and bladder, the external iliac vein will be ligated and divided, the crest of the ilium and sacroiliac synchondrosis skeletonized by dividing the overlying muscles and the innominate bone disarticulated (insert)

The incision is then curved posterior and inferior, over-riding the greater trochanter and extending along the infragluteal fold to join the anterior incision at the symphysis pubis.

This incision extends more superiorly than that usually described^{2, 3} and it permits good retraction of the peritoneal contents out of the field of surgery. It affords an excellent exposure for exploratory celiotomy when indicated (Case 3) and permits resection of the paraortic lymph nodes to the level of the renal vessels (Case 8).

Anterior dissection (Fig 1) After deepening the anterior incision Por-

part's ligament is divided and the inferior insertion of the rectus abdominis is severed from the pubic bone. The peritoneum is easily separated from the iliac fossa and the spermatic cord, bladder and rectum are then retracted out of the field and the ureter identified. The external iliac artery and vein are clamped, cut, and doubly ligated.

The practice of postponing ligation of the iliac vein in order to permit the salvage of blood from the lower extremity² is not recommended, because the trauma incident to operative manipulation may contribute possibly to intravascular dissemination of the neoplasm, especially in lesions about the vessels. Accordingly, after ligating the external iliac artery just inferior to the bifurcation of the common iliac artery, the involved extremity is raised for a few moments to permit some blood drainage and the external iliac vein is doubly ligated and severed.

The crest of the ilium is skeletonized after severing the iliopsoas muscle high and the bony attachment of the quadratus lumborum muscles. After severance of the iliacus, Gemelli, pyramiformis and levator ani muscles, the sacro-iliac synchondrosis is exposed.

The symphysis pubis is now skeletonized and transected with a Gigli saw and the sacro-iliac synchondrosis is next divided by means of a Gigli saw inserted through the sciatic notch.

In certain instances where difficulty may be encountered in inserting the saw through the sciatic notch, this phase of the operation may be postponed until the posterior dissection. After the sacroiliac synchondrosis is skeletonized by severing the posterior musculature, it can be easily transected by means of the Gigli saw passed through the sciatic notch. During our first four procedures a chisel was used to separate the sacroiliac synchondrosis but it was found that a saw is much less traumatic. The actual disarticulation appears to be a critical point of the operation and at this point three patients of the eight suffered marked drops in blood pressure. Accordingly, when the actual disarticulation is to be performed, the anesthetists are instructed to administer whole blood at a brisk rate.

Bleeding from the exposed bone edges is controlled with Gelfoam or bone wax.

Posterior dissection. The patient is turned laterally to the uninvolved side and the posterior phase of the operation is performed. The gluteal muscles, the sacrotuberous, ilio-lumbar and sacrospinalis ligaments are severed. The gluteal and obturator vessels are identified and ligated. Manipulation of the extremity during the posterior dissection facilitates identification of the various structures. The nerves of the lumbar and sacral plexus are transected when encountered and are not injected. The extremity is now attached only by the sciatic nerve which is severed last.

The skin edges are approximated with number 2 silk sutures, and a drain inserted through a stab wound. A pressure bandage is applied. Split thickness skin grafts may be applied directly if the loss of skin precludes primary closure.

In those instances where there is certainty that the skin of the lower extremity is not diseased, dermatome drums of skin are removed from the resected

specimen and preserved in the ice box. Then if wound breakdown does occur, skin is available for grafting. This method was utilized with success in Case 4.

Postoperative care After removing the temporary anal suture, a rectal tube is usually inserted for the first two days postoperatively.

Tidal bladder drainage is instituted and continued for about four days.

The patient remains on a full course of antibiotics and Wangensteen drainage via a Levine tube in the stomach is routinely used during the immediate postoperative period.

Frequent and large transfusions may be necessary to combat an anemia which may be quite severe. The anemia results not only from the operative loss of blood but also the removal of a large amount of erythropoietic tissue. The anemia has not persisted longer than two weeks in this series.

Early ambulation is encouraged and the patient instructed how to bear all weight on the one ischial tuberosity.

Postoperative complications (1) *Genito-urinary and gastro-intestinal* There have been no complications in the normal activity of urination or defecation. In one patient (Case 4), the posterior wound was drawn taut placing the anus on a bias but this did not produce any discomfort. No bladder or rectal infections developed. Prophylactic use of Wangensteen suction prevented abdominal distention.

Any existing sexual function has not been compromised in any patient in this series. The wife of one patient is now pregnant.

Judin's patient became pregnant and had a normal delivery following the operation.¹⁰

(2) *Phantom limb* This objectionable complication was encountered in four patients of this series. Usually the degree of symptoms before surgery dictated the severity of "phantom limb" pain. One patient (Case 5) on whom the operation was performed for palliation suffered so severely from phantom limb pain that any benefit from the operative procedure was negated.

(3) *Herniation* No hernias have been observed in this series. The peritoneal cavity is well supported by fascia and skin, hence the retention of the gluteus maximus for this purpose or the utilization of other supporting measures is not necessary.¹⁶

Wound separation and postoperative infection This has been the most frequent complication encountered in our series, occurring in four of the eight operations. In three cases a rapid healing occurred which appeared complete in ten days after surgery. In three patients (Cases 2, 5, and 7) the complication can be attributable to the fibrosis and compromise of healing ability of tissue resulting from previous irradiation.

In no instance did the wound separation and corresponding local infection produce severe complications and in all instances the infection was satisfactorily controlled and the wound secondarily closed with the aid of skin grafts.

Osteomyelitis Pack and Ehrlich caution against severing the pubic bone anywhere except through the symphysis because the exposed cancellous bone may be a locus for future infection.²



FIG 2—*Case 1* Roentgenogram of pelvis demonstrating osteolytic lesion of right ilium resulting from an Ewing Endothelioma. The photograph on the right is a postoperative roentgenogram demonstrating absence of right innominate bone.



FIG 3—Surgical specimen of *Case 1*. Bulky Ewing Endothelioma arising in the ilium and infiltrating gluteal region.

DISARTICULATION OF AN INNOMINATE BONE

CASE REPORTS

Case 1 —C R—Ewing tumor involving right buttocks and ilium

The patient is a 26-year-old white male who noted rapid fatigability and vague pains in the right lower extremity of four months duration. There was in addition, swelling of the right buttock of two months duration. The patient had no other symptoms.

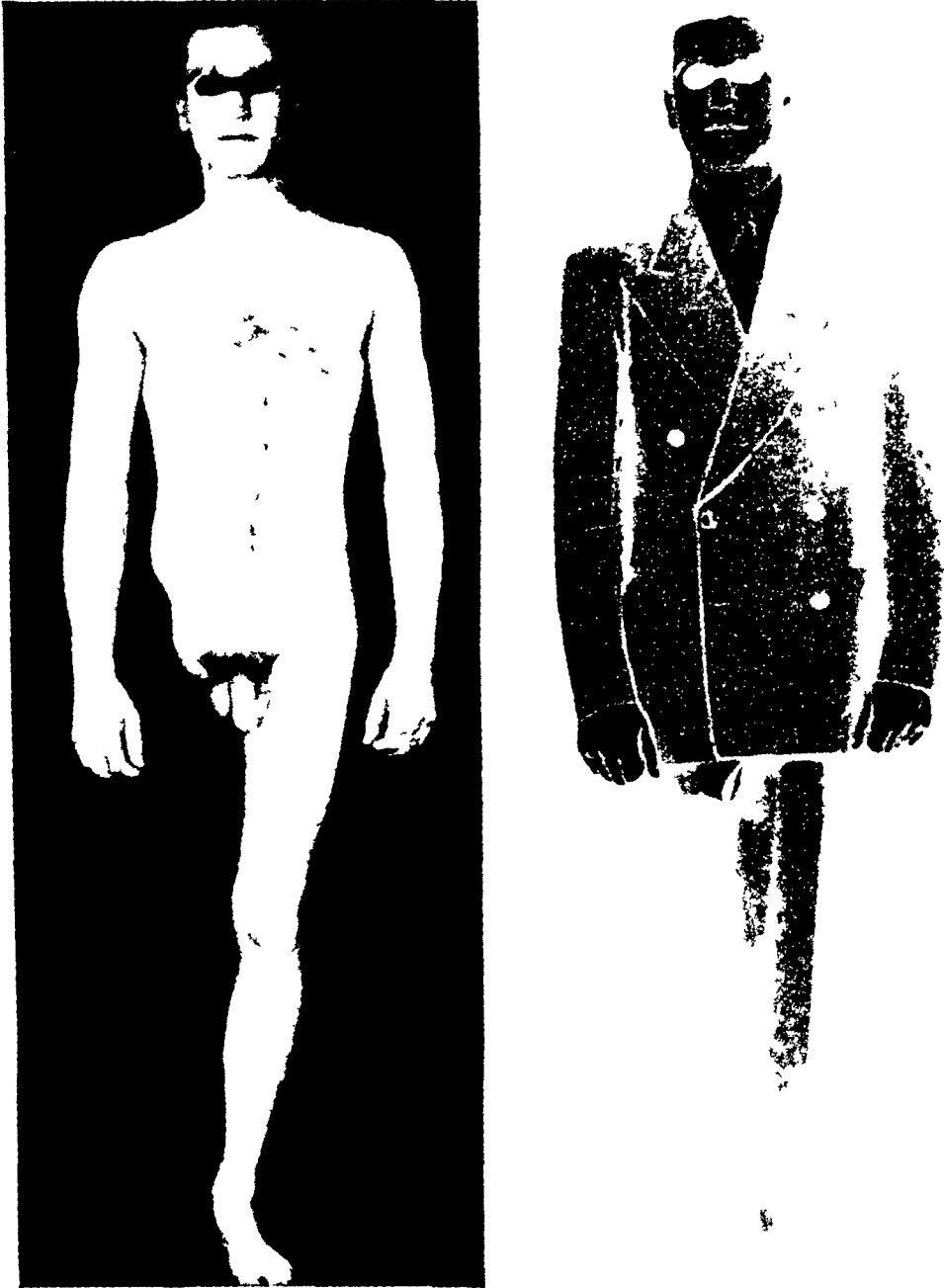


FIG 4—Photograph of patient (Case 1) five months following hemipelvectomy.

Physical examination on September 12, 1946, was negative except for a large, diffuse non-tender mass involving most of the right gluteal region and measuring 8 x 12 cm. The overlying skin was distended and of a pinkish hue.

Radiographs revealed invasion of the right ilium extending toward but not involving sacro-iliac synchondrosis (Fig 2). Roentgenograms of the chest were negative for metastases and all laboratory studies were within normal limits.

A biopsy of the gluteal mass was reported anaplastic sarcoma

On October 28, 1946, a right hemipelvectomy was performed and the patient made an uneventful postoperative recovery. The resected specimen revealed the entire right posterior region to be replaced by a hemorrhagic, partially necrotic mass with poorly defined borders (Fig 3). The iliac bone was invaded by tumor.

The patient remained asymptomatic but on July 22, 1947, follow-up roentgenograms of the chest revealed bilateral metastasis. He was given a course of Coley's toxin therapy consisting of 14 daily intravenous injections of the toxin, starting November 8, 1947. The initial dose was 1/100 minum and succeeding doses were gradually increased until a maximum dose of four minums was reached which was repeated four consecutive days. Roentgenograms revealed an increase in the metastatic deposits in the lungs. He remained asymptomatic until April 8, 1948, when he developed a persistent, productive cough, right chest pain, and dyspnea. Thoracentesis yielded 3240 cc of hemorrhagic fluid.

This patient is living at the present time with bilateral pulmonary metastases. He is relatively asymptomatic but is receiving deep roentgen ray therapy to the pulmonary metastases.



FIG 5—Case 2. Preoperative appearance one and one-half years after partial amputation of penis for carcinoma and repeated fulgerations and x-ray treatments to metastases in right groin which were deeply infiltrative. Left inguinal nodes also contain metastases.

Comment. An attempt to treat a massive Ewing's tumor by radical surgery succeeded in controlling the primary lesion but pulmonary metastases became clinically manifest nine months after the resection.

The patient is relatively asymptomatic one year and nine months subsequent to operative intervention and one year after the appearance of pulmonary metastases.

Case 2—J. P. Right hemipelvectomy and radical groin dissection of opposite side for metastases from carcinoma of penis.

The patient, a 54-year-old colored male, was admitted to the hospital in February, 1946, with a diagnosis of carcinoma of penis with right iliac lymph node metastases. He

was treated by a partial amputation of the penis and deep x-ray therapy and fulgeration were administered to the iliac metastases. During the subsequent year and a half, repeated attempts to control the metastases with irradiation and cauterly excision were without benefit.



FIG 6—*Case 2* Gross appearance of operative specimen demonstrating infiltrating metastases

When first observed by the authors on February 24, 1947, the patient presented a large mass involving most of the right groin and measuring 10 cm in diameter. It was hard and board-like in character. It was intimately bound to the underlying structures,

and presented the appearance of carcinoma and X-radiation reaction. In the center of the board-like area was an ulceration measuring 3 cm in diameter, consisting of a dirty grey foul granulating surface (Fig 5).

In the left inguinal region were many hard freely movable lymph nodes measuring 2 to 4 cm in diameter.

The patient refused surgery but returned four months later with the right groin severely infected. After a careful preoperative regime, a right hemipelvectomy was performed on July 28, 1947. The patient went into surgical shock during the operation which was combatted by transfusions. His postoperative course was uneventful.

The superficial and deep iliac nodes were found involved by metastases. The neoplasm had extended to the soft tissues of the groin and had extensively infiltrated the contiguous muscles (Fig 6). The irradiation fibrosis obscured the planes of clearance.

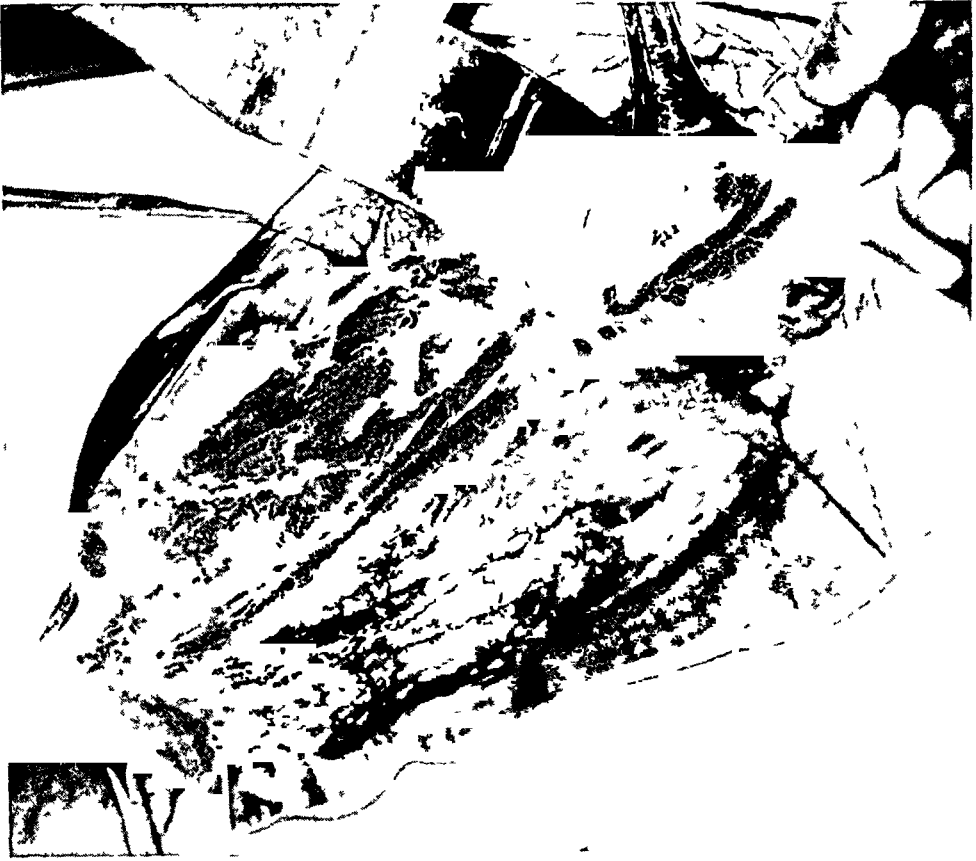


FIG 7—Case 2 Left radical groin dissection demonstrating iliac and femoral vessels and the inguinal region stripped of lymph node metastases.

Postoperatively he developed a slough of the flaps and wound infection. It was felt that the repeated attempt at cautery excision and the deep irradiation contributed to the slough.

He was given supportive therapy, antibiotics, and moist dressings which controlled the infection.

On August 21, 1947, a left radical groin dissection and closure of the defect resulting from the right hemipelvectomy was performed. Superficial and deep iliac lymph nodes were found infiltrated with cancer. The procedure was tolerated well (Figs 7 and 8) and the resultant defect in the suprapubic area was closed with a split thickness dermatome graft.

At the present time, this patient is clinically free of tumor.

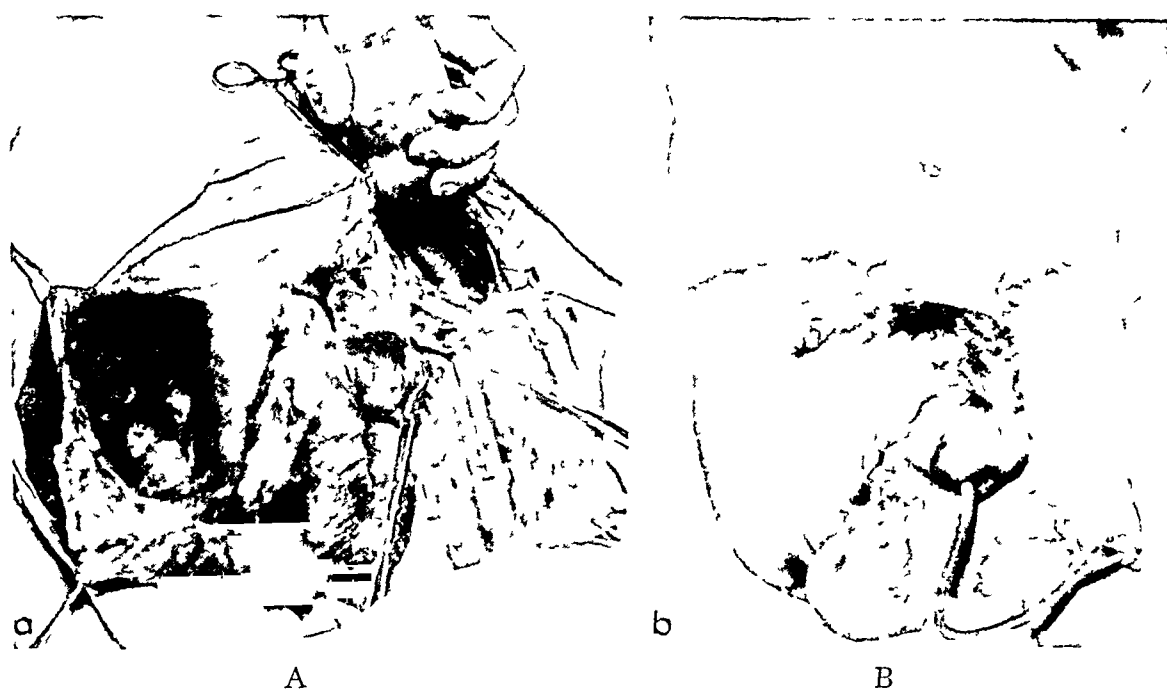


FIG 8—Case 2 (A) Left radical groin dissection and opened wound from previous right hemipelvectomy prepared for closure (B) The closure has been completed



FIG 9—Case 3 (A) Operative specimen demonstrating testicle, spermatic cord and portions of peritoneum which were infiltrated by the bulky synovial sarcoma

Comment This represents a case of squamous carcinoma of the penis treated primarily by partial amputation of penis. Two years later a right hemipelvectomy and left radical groin dissection were performed for persistent tumor. Bilateral groin metastases have remained controlled for one year. Previous attempts to treat the groin metastases with irradiation and local excision were without effect.

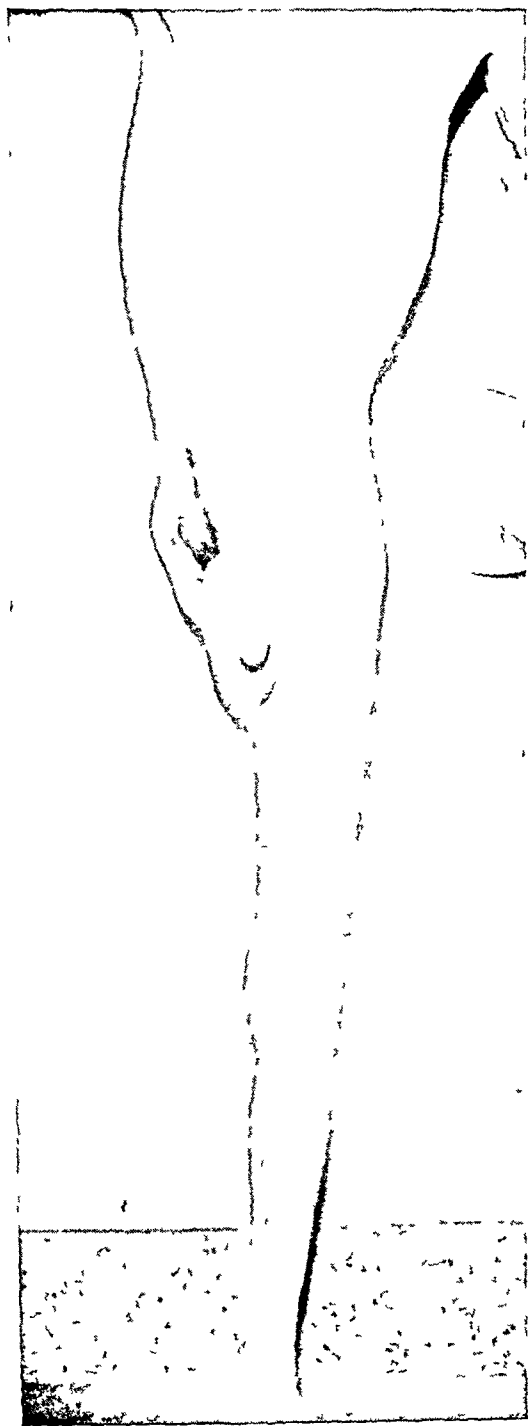


FIG 10—Case 3 (B) Postoperative photograph demonstrating the high incision necessary to resect involved peritoneum. Slight separation of wound edges occurred.

Case 3—P A W Synovial sarcoma of right upper thigh

This patient was a 36-year-old white male who first noted a walnut sized mass in the right upper thigh in 1945. It remained quiescent for one year and on November 7, 1946, a local excision was performed elsewhere, followed by postoperative irradiation. The factors of irradiation are not known. An ulcerated area of the upper thigh persisted and an inguinal mass subsequently developed.

The patient was admitted to Veterans Administration Hospital, Hines, Illinois, March 24, 1947, at which time he presented an ulceration 2 cm in diameter, 6 cm inferior to Poupart's ligament. A subcutaneous mass was present in the subinguinal area. Numerous enlarged superficial inguinal lymph nodes were palpable. The tumor extended above Poupart's ligament for an indeterminate distance. A biopsy was interpreted as synovial sarcoma. All laboratory findings were normal and a chest roentgenogram negative for metastases.

Operation A hemipelvectomy was performed on April 23, 1947. It was noted that cancer had grossly invaded all deep iliac lymph nodes and infiltrated into the peritoneum. Large masses of friable intra-abdominal tumor tissue were resected including the peritoneum, part of prostate, spermatic cord structure, and testicle (Fig 9).

The patient tolerated the operative procedure well and his immediate postoperative course was uneventful except for slight necrosis of the posterior skin flap (Fig 10). Two weeks postoperatively he developed evidence of intraabdominal cancer and succumbed July 3, 1947, due to generalized visceral metastases.

Comment A malignant synovial sarcoma of the thigh had produced diffuse generalized visceral metastases from which the patient succumbed two months following hemipelvectomy

Case 4—T G Fibrosarcoma left iliac region unsuccessfully treated by irradiation

This 51-year-old white male dated the onset of his symptoms from March, 1946, when he noted a vague aching in upper left thigh region. Two months later he noted a



FIG 11—*Case 4* Photograph demonstrating increased circumference and ulceration of left thigh due to diffuse fibrosarcoma which infiltrated to the hip joint. Previous irradiation therapy had been administered.

gradual increase in the circumference of the thigh. There was no weight loss. Biopsy of the left thigh established the diagnosis of fibrosarcoma. The patient was given thirty deep x-ray treatments elsewhere during August and September, 1946, with mild relief (The irradiation factors could not be obtained).

On admission to the hospital February 1, 1947, the patient was well nourished but there was a diffuse, firm enlargement of the upper left thigh. The skin over this area was pigmented. There was a shallow ulceration 2 cm in diameter with sloping margins and a dirty grey base on the anterior aspect of the pigmented area (Fig 11). All laboratory data was negative and chest x-rays revealed no evidence of pulmonary pathology.

On February 17, 1947, a left hemipelvectomy was performed and a large tumor mass

involving the musculature of the upper thigh, extending inside the retroperitoneal area and intimately adherent to the external iliac vessels

The patient tolerated the procedure well but developed postoperative separation of the wound edges necessitating skin grafting

On May 15, 1947 (three months postoperatively) the patient developed cough and chest pain. Pulmonary metastases were demonstrated by roentgenographic studies. Palliative irradiation was without effect and the patient succumbed July 10, 1947. Autopsy revealed massive hemorrhagic pulmonary metastases involving approximately two-thirds of the pulmonary parenchyma. No signs of any other cancer were observed.

Comment A fibrosarcoma of left thigh was treated by irradiation without effect. Six months after irradiation therapy a hemipelvectomy extirpated the local disease but the patient succumbed five months postoperatively due to pulmonary metastases. It is of interest to conjecture what the preoperative delay may have contributed to the final outcome.

Case 5—J. D. Palliative resection for diffuse melanosaarcoma

The patient is a 28-year-old white male. He had a small brown mole measuring $\frac{1}{2}$ cm in diameter on the anterior lower right leg locally excised in October, 1945. The excision was incidental to reconstructive surgery which was performed in Luzon subsequent to gunshot wounds to the right leg.

One year later a mass developed in the right inguinal region which had gradually increased in size. The inguinal mass was excised and the diagnosis of "cancer" made. Five x-ray treatments were given but the factors of irradiation are not known. However, the mass in the inguinal region grew rapidly in size and the patient developed numerous painless subcutaneous nodules varying from 1 to 3 cm in diameter.

On admission, June 12, 1946, the patient presented a large irregular tender, hard, and fixed mass in the right inguinal region. It was firmly attached to all surrounding structures and the overlying skin was telangiectatic, erythematous and shiny. The area was exquisitely tender. The patient also presented numerous subcutaneous nodules. He was emaciated and in extreme pain. The following palliative procedures were attempted: (1) Vigorous estrogenic therapy, (2) a course of methyl-bis (nitrogen mustard) therapy and (3) local deep x-ray therapy. The severe pain in the groin, radiating down the leg, persisted.

Accordingly, on July 30, 1947, a palliative right hemipelvectomy was performed and the patient made an uneventful postoperative recovery. However, the symptoms due to the "phantom limb" vitiated any benefit from operative procedure. The patient succumbed from generalized melanosaarcomatosis on September 28, 1947.

Comment A palliative procedure was performed and a foul smelling, ulcerated infected tumor was removed which had caused the patient severe pain that did not respond to medical management.

The ensuing phantom limb negated most of the benefits expected from the resection.

Case 6—E. C. R. Periosteal fibrosarcoma of right femur

This 26-year-old white male was perfectly well until May, 1946. While in China with the Marines, he noted pain in the right hip and immediately consulted his surgeon. Two weeks later the pain which had previously been localized to the hip began to radiate down the leg to the knee, causing limited motion of the right knee and hip. In January, 1947, x-rays were taken and diffuse osteoporotic lesion was diagnosed "septic arthritis." The hip and knee were then placed into a cast. In February, 1947, the patient complained of severe pain in the chest, and fever. He was hospitalized for two months and treated

DISARTICULATION OF AN INNOMINATE BONE

with penicillin and was said to have had pleurisy. At that time he lost 20 pounds of weight in two months. In April, 1947, because of the persistence of difficulty with his hip joint and leg he was placed in a body brace. In May, 1947, x-rays were taken and the osteolytic lesion of his hip was said to have extended and the patient was placed in a plaster spica. In July, 1947, repeated x-rays were taken which showed osteolysis of the right hip. An aspiration biopsy was taken on July 15, 1947, and an immediate pathological report was obtained of sarcoma, either a fibrosarcoma or a synovial sarcoma. X-rays of the right hip revealed a marked osteolytic lesion involving the head and neck of the femur (Fig 12).



FIG 12—Case 6 Roentgenograph demonstrating infiltration of fibrosarcoma into hip joint and femur

Physical examination revealed a large mass in the right inguinal region. The overlying skin was neither adherent nor invaded. The mass extended to involve most of the hip joint, extending to Poupart's ligament and to the anterior surface of the right upper thigh. Along the margin of the mass a small freely movable lymph node was palpated.

A hemipelvectomy was performed on July 21, 1947. The resected specimen presented a large circumscribed mass which was greyish in color and involved most of the retroperitoneal space, invading the anterior musculature of the thigh (Fig 12). The tumor mass infiltrated the neck and head of the femur and involved the acetabulum. The patient withstood the procedure well and remained asymptomatic except for pain of unknown etiology in the left hip until September 18, 1947, when he developed an acute hepatitis from which he recovered.

In January, 1948, the patient developed chest pain, a dry unproductive cough and dyspnea. A roentgenogram of the chest revealed a massive left pleural effusion and

multiple metastases to the right lung. He was given a course of Caley's toxin with little relief. Repeated thoracentesis yielded large quantities of serosanguineous fluid.

The patient succumbed April 9, 1948, and autopsy revealed massive pulmonary metastases. No evidence of local recurrence was observed.

Comment Disarticulation through the sacro-iliac synchondrosis was necessary to remove this neoplasm which had invaded the hip joint. Although the neoplasm was surgically resectable, death occurred 8 months postoperatively.



FIG 13—Case 6 Operative specimen showing bulky fibrosarcoma which had invaded hip joint

due to extensive pulmonary metastases. It is lamentable that one year elapsed from the onset of symptoms until the patient received definitive treatment.

Case 7—B. L. M. Metastatic hypernephroma

The patient was a 48-year-old white male who first noted pain in the region of the left hip on weight bearing, in November, 1946. He was treated with various non-specific remedies until June 7, 1947, when roentgenographs revealed a destructive process of the left ilium. A biopsy specimen was interpreted as sarcoma, either reticulum cell sarcoma



Fig 15—Case 7 Photograph of innominate bone which has been detached from the remainder of the surgical specimen demonstrating the osteolytic metastatic hypernephroma



Fig 14—(Case 7) Roentgenogram of pelvis demonstrating osteolytic character of metastatic hypernephroma

or angiosarcoma. The patient was given a course of deep x-ray therapy from July 10, 1947, to August 14, 1947, for a total dose of 3,000 roentgens to the left ilium posterior and 3,000 roentgens to left lateral ilium with the following factors: 250 KV, 2 mm copper filtration, 80 cm target skin distance, estimated tumor dose 3675 roentgens, with slight regression in the size of the mass.

On October 1, 1947, a left hemipelvectomy, which included a portion of the sacrum, was performed. The resected specimen demonstrated a large mass of hemorrhagic neoplastic tissue measuring 8 x 7 centimeters and destroying the ilium (Fig 15). Microscopic sections from the surgical specimen revealed the neoplasm to represent a metastases from a primary kidney carcinoma.

The patient has made an uneventful postoperative recovery with the exception of a painful sinus which was debrided and healed completely. At present the patient reveals no evidence of disease. Complete genito-urinary studies, including peri-renal air insufflation are normal.

Comment. Radical surgery was performed on this patient because of the mistaken impression that the neoplasm of the ilium was primary in bone. Careful study by several pathologists revealed the neoplasm to be a metastases from a primary renal cancer. The patient is well one year postoperatively. It is planned to explore the kidneys.

This case resembles Sugarbaker's and Ackerman's case number 3.¹

Case 8—Squamous carcinoma of left lower leg, developing on a burn scar and producing fixed superficial and deep inguinal metastases.

The patient was a 24-year-old white male who suffered gasoline burns of lower left leg, right thigh and left lower arm in 1936. The wounds required two years to heal and he remained well from 1938 to 1947, at which time the scar of the left lower leg ulcerated and the ulcerated defect continued to enlarge.

He was hospitalized elsewhere for 142 days receiving local treatment, attempts at plastic repair and a simple excision of lymph nodes in the left inguinal region.

On admission to University Hospitals, University of Minnesota, on August 8, 1948, he presented a large fungating tumor mass measuring 23 x 12 x 1 cm and extending from the left popliteal space inferiorly to involve most of the left lower leg. The surface was granular with heaped up edges. Biopsies from various areas were reported squamous carcinoma.

In the left inguinal region were numerous firm fixed masses which measured 3 to 4 cm in diameter. They had coalesced to produce a large irregular mass. There was a recent surgical scar over this inguinal mass.

The patient presented, in addition, old burn scars involving the right lower extremity and right upper extremity which were well healed. An inferior venacavogram outlined the inferior vena cava and there was no evidence of extrinsic or intrinsic pressure.

On August 20, 1948, the deep iliac region was explored through an incision which extended from the parallel to the inguinal ligament to a point about 3 cm superior to the anterior superior spine.

The deep iliac nodes were noted to be infiltrated with cancer and adherent to contiguous structures. Accordingly, a sacroiliac disarticulation was performed in conjunction with Dr. Arnold Kremen. A dissection of the periaortic nodes on the involved side to the level of the renal pedicle preceded the hemipelvectomy.

The patient withstood the procedure well and his postoperative course was uneventful.

The pathologic specimen revealed the deep iliac region involved with a large mass of necrotic tumor tissue which completely surrounded the femoral artery and vein and infiltrated the walls of the vessels. The periaortic nodes did not reveal evidence of cancer and there were no popliteal lymph nodes involved by the neoplastic process.

Comment A hemipelvectomy was necessary for this squamous carcinoma of the lower leg which developed on an old burn scar and produced superficial and deep iliac metastases which had infiltrated to the soft structures of the pelvis and invaded the walls of the external iliac artery and vein

DISCUSSION

Operative Mortality There has been a steady and progressive decline in the operative mortality for hemipelvectomy. In 1909 the mortality rate when performed for cancer was 67 per cent¹³ and Pingle in 1916 remarked on the achievement in decreasing the mortality rate to 56.6 per cent in the intervening years.¹³ In 1935 the operative mortality of all cases performed to that date was 60 per cent.¹

In the subsequent ten years, 80 additional cases were collected and the reported mortality rate of that series was 18 per cent.⁴

Recent reports by Morton, 4 cases⁵, Pack and Ehrlich, 7 cases², and this series, 8 cases without an operative death suggests that the technic of conducting the patient safely through a hemipelvectomy has been achieved. Adequate pre- and postoperative care and special emphasis on supportive therapy (transfusion) during the operation, are the major factors contributing to the precipitous drop in the operative mortality rate.

There is nothing to suggest that the patients of the three series cited above were better operative risks than in previously reported series, in fact, two patients were critically ill from widely disseminated cancer and the operative intervention performed for palliation.²

PROGNOSIS

In this series the end results are not good. Four patients have succumbed. In one patient where the operation was performed for palliation, the patient succumbed two months postoperatively of diffuse melanosarcomatosis.

One patient, who had intraperitoneal invasion of a synovial sarcoma at the time of surgery, expired two months postoperatively with generalized visceral metastases (Case 3).

Two additional patients succumbed five months and eight months postoperatively due to diffuse pulmonary metastases resulting from a spindle cell fibrosarcoma and synovial sarcoma respectively (Cases 4 and 6).

A fifth patient has bilateral pulmonary metastases 24 months subsequent to surgery (Case 1) and the remaining three patients are apparently free of disease two, 12, and 15 months respectively after surgery (Cases 2, 7 and 8).

In none of the patients that expired were local recurrences observed as observed by postmortem examination.

Further review of this series reveals that in all seven cases where the operation was performed for curative purposes, there was a delay varying from seven to 19 months from the onset of symptoms. The average delay of the group was 10.4 months (Table I). Moreover, the delay in certain instances was attributable to the medical profession. In two instances (Cases 6 and 7), a proper diagnosis was not established and no definitive therapy instituted for

prolonged periods. In three instances, adequate therapy was delayed while conservative surgical measures or radiation therapy were attempted by other physicians (Table I).

It is probable that the delay in addition to the trauma of ineffective therapy contributed significantly to the undesirable results in four patients of this series.

It is difficult to adjudicate the true accomplishment of exarticulation of the pelvis from published reports because of the inadequacy of the data. Pack and Ehrlich state that one-third of the patients who submitted to the operation

TABLE I — *Resume of 8 Patients on whom Hemipelvectomy was Performed—
Author's Series*

Patient	Age	Pathologic Diagnosis	Previous Treatment	Delay Before Operation	Duration From Operation Until Metastases Occurred	Remarks
(1) C R	26	Ewing's tumor of right gluteal region, and right ilium	None	7 months	9 months	Alive 24 months after operation. Bilateral pulmonary metastases present.
(2) J P	54	Squamous carcinoma of penis with bi- lateral groin metas- tases	(1) Partial amputation of penis (2) Deep x-ray and cau- tery excision right in- guinal metastases	1 year 5 mo	0	Patient well 15 months after right hemipelvec- tomy and left radical groin dissection.
(3) P A W	36	Synovial sarcoma anterior inguinal region	Local excision and deep x-ray	8 months	2 weeks	Died 2 months after surgery. Diffuse vis- ceral metastases.
(4) T G	54	Fibrosarcoma ante- rior inguinal region	Deep x-ray	10 months	3 months	Died 5 months follow- ing surgery. Pulmo- nary metastases.
(5) J R D	28	Melanosarcoma generalized	None	Palliative procedure in patient with general- ized melanosarcoma		Died 2 months post operatively. No pallia- tion.
(6) E C R	26	Periosteal fibrosar- coma anterior in- guinal region	Prolonged symptomatic treatment	12 months	5 months	Succumbed 8 months after surgery from ex- tensive pulmonary metastases.
(7) B L M	48	Metastases from kid- ney carcinoma to left innominate bone	Symptomatic and deep x-ray therapy	7 months		Patient well 12 months after surgery.
(8) A B	24	Squamous carcino- ma of leg with in- guinal metastases	Local excision of in- guinal metastases	12 months		Patient well 4 months after surgery.

because of malignant disease were reported clinically cured, but state further that the follow-up in most instances was most inadequate.²

A perusal of the literature reveals nine instances of five-year survivals with the following histologic diagnoses⁴

Chondrosarcoma	3 patients
Chondroma	1 patient
Osteoclastoma	1 patient
Osteogenic Sarcoma Ilium	1 patient

Extraperiosteal Sarcoma	1 patient
Spindle Cell Sarcoma	1 patient
Epidermoid Carcinoma	1 patient ¹⁵

It is suggested that the low survival rate of reported cases may be the result of the following factors

- 1 The previous high operative mortality rate
- 2 Certain neoplasms known to be radioresistant (spindle cell sarcoma, synovial sarcoma) received irradiation as the method choice instead of surgical intervention. When hemipelvectomy was instituted finally, there had been a prolonged delay.
- 3 Conservative surgical procedures were attempted frequently before resorting to radical resection. The less radical procedures were utilized first because (a) they were being appraised, (b) the surgical inexperience of the physician precluded his performing a major procedure, (c) the humane attempt of trying to spare the patient the mutilation resulting from hemipelvectomy and (d) the erroneous policy of trying a more conservative method first to see what it may accomplish before resorting to the radical curative procedure. One may be more conservative in the long run frequently by being radical at the outset.
- 4 Attempts to retain partial function have led certain surgeons to spare tissue which should have been resected. Sugarbaker and Ackerman¹ stress this feature and have collected from the literature eight patients who developed stump recurrences. They point out that in four cases the innominate bone was incompletely severed and in one instance the gluteus maximus was preserved.

PROGNOSIS AND HISTOLOGIC TYPE

- 1 Bulky benign lesions such as chondromas, osteochondromas, neurofibromas, offer the best prognosis^{1, 6}
- 2 Malignant neoplasms, of low grade malignancy of bone (Chondrosarcoma)^{5, 17} or well differentiated malignant neoplasms of soft tissue (myxoliposarcoma, periosteal fibrosarcoma, extra-osseous osteogenic sarcoma) should offer a good prognosis⁴
- 3 Osteogenic sarcoma of the innominate bone or extension from the femur into the hip bone do not offer a very good prognosis²³. Cures, however, have been reported⁴
- 4 Primary epidermoid carcinoma arising from the skin of the groin and infiltrating deeply¹⁵ or metastases from carcinoma which infiltrate inguinal tissues (Case 2) may offer a good prognosis in certain instances.
- 5 Sarcoma of soft tissue, especially fibrosarcoma, rhabdomyosarcoma and synovial sarcoma are the histological types for which hemipelvectomy has been performed most frequently and which has produced poor end results (3 cases of this series). Of 25 cases labelled sarcoma observed in the literature there is only one recorded instance of a five-year survival rate^{4, 14, 18, 21}. These figures should not deter one, however, from the performance of radical surgery where it is the only method that may completely extirpate the disease.
- 6 Hemipelvectomies have been performed for Ewing sarcoma and multiple myeloma, but no cures have resulted^{18, 19}

SUMMARY

In 1916 J. Hogaith Pingle, an English surgeon who pioneered and developed exarticulation of the innominate bone, stated "There has scarcely been a single operation of any magnitude that has not in the early stages of the development been looked at askance, and the inter-pelvi-abdominal amputation must always remain one of the severest in surgery. But, if the real nature of these cases can be recognized at an early stage and the operation can be carried through before the patients have commenced to run down in consequence of the disease, the mortality following will, I believe, be so far diminished that justification of the operation will in the future be generally admitted."

Pingle's prophecy has been accomplished and inter-pelvi-abdominal amputation is today a safe procedure. Emphasis must be placed on utilizing this procedure with dispatch where indicated.

CONCLUSIONS

1. Disarticulation of an innominate bone and its subjacent extremity have been performed 158 times (exclusive of this report) since the first successful resection 52 years ago.

2. The operative mortality has declined steadily from 67 per cent in 1909 to 56.6 per cent in 1916 to 18 per cent in 1945. In two recent series, Pack and Ehrlich (7 cases) and this report (8 cases), no operative deaths occurred. Careful pre- and postoperative care and adequate transfusions during the operation have contributed significantly toward reducing the hazards of hemipelvectomy.

3. Eight cases where hemipelvectomies were performed to ablate cancer are presented. The preoperative preparation, surgical technic, postoperative complications and their prevention are discussed.

4. The end results of disarticulation of the innominate bone for cancer are not good. Nine instances of five-year survivals are observed in the literature (the follow-ups of many reported cases are not presented frequently).

Of the eight cases reported in the series, one was performed for palliation (melanosarcoma)—one patient succumbed two months postoperatively (synovial sarcoma) from visceral metastases—two patients succumbed from pulmonary metastases (one with fibrosarcoma in five months, and one periosteal fibrosarcoma in eight months)—one patient with Ewing's tumor has pulmonary metastases 24 months following surgery and three patients are apparently free of disease.

Note. Since the manuscript was prepared for publication three additional hemipelvectomies have been performed.

Case 1 is a 35-year-old white male for whom a mid-thigh amputation was performed for a fibrosarcoma about the left knee joint. Because of radiological evidence of sarcoma about the hip joint, a hemipelvectomy was performed and the patient is well and apparently free of disease one year postoperatively.

Case 2 is a 32-year-old white male for whom a hindquarter amputation was performed for a chondrosarcoma involving the head of the left femur and producing a bulky gluteal mass. Symptoms had been present for one and one-half years. The patient is

well six months postoperatively except for a low grade osteomyelitis of the opposite pubic bone

Case 3 is a 38-year-old white female who weighed 203 pounds. She had pain of the left thigh of two and one-half years duration, and a fracture one year before admission. A massive neoplasm involving the proximal femur, left hip joint, and medial aspect of the thigh necessitated a hemipelvectomy. The histological diagnosis was chondrosarcoma, with invasion of the femoral vein and erosion of femur. Her obesity precluded good wound healing and a period of about two months were required before the patient walked. She is well and apparently free of disease two years after surgical intervention.

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TALC GRANULOMA — A SURVEY OF ITS INCIDENCE AND SIGNIFICANCE*†

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IN THE 14 YEARS since Antopol first described the entity known as talc granuloma, numerous clinical and experimental studies have been reported in the literature. However, there has been an inertia on the part of the medical profession to accept the challenge of the danger of the use of talc. In spite of what has been written practically all hospitals, save those where the problem has been made a special study, are still using talcum powder as a dusting powder for their surgical rubber equipment.

It was not until we had a death at our hospital from intestinal obstruction and fecal fistula directly attributable to talc (reported by Dr A J Swingle¹⁸), that we became fully aware of the seriousness of the practice of using talcum powder in the operating room. This case instigated our consideration of the statistical incidence of talc granuloma as a postoperative complication. Although a review of the literature revealed many cases resembling those we subsequently found, there was no instance in which a comprehensive survey was made of the incidence of the disease in routine surgical material in a given hospital, to correlate this with total operative procedures performed. With this question in mind we reviewed the consecutive surgical pathologic material submitted to the laboratory over the past 16 months. Not only were we interested in the incidence of occurrence, but also if possible to correlate the presence of talc granuloma with actual morbidity.

HISTORY

It is not the purpose here to completely review the literature on this subject. This has previously been thoroughly done by Seelig *et al*,¹⁷ and others subsequent to Antopol's first paper in 1933. Knowledge of the effect of talc in tissues has been gradually developed. Erb³ in 1935 reported six cases of dusting powder granuloma. However, he did not report lesions produced by talc crystals, his cases being due to lycopodium spores. Owen¹³ in 1936 reported one case of talc granuloma which caused intestinal obstruction two years following appendectomy. In 1940 German⁵ reported a case of lupoid-sarcoid reaction induced by a foreign body (silica) and in 1943 this same author⁶

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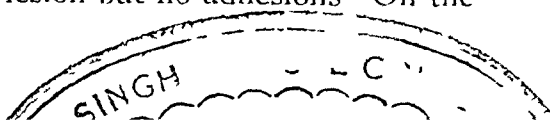
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presented a series of 50 talc granulomata, 40 of which were intra-abdominal and were found in patients undergoing abdominal surgery for at least the second time. He further found that if serial sections are routinely taken through the omentum of patients previously operated upon, granulomata will almost always be found. In many of his cases the talc was merely an incidental finding and not necessarily the cause of any complaint. Ramsey and Douglass,¹⁴ McCormick and Ramsey,¹¹ Byron and Welch,² and Ramsey¹⁵ all have reported additional cases, and the injury now has been described in various parts of the body, including intra-peritoneal, intra-thoracic and in skin lesions, scar nodules and tumor masses, in vaginal, rectal, brain, spinal, kidney, breast, ovary, testes, penile and parts and in healing surgical wounds, *et cetera*, Lichtman *et al*^{9, 10} found granulomatous lesions in malfunctioning intestinal stomata, and demonstrated experimentally the importance of talc as the causative factor in the production of fistulas. Swingle¹⁸ has reported a case of a patient from this hospital who had a laparotomy for removal of an abdominal tumor and then had 14 subsequent laparotomies and finally expired from intestinal obstruction and fecal fistula caused as a direct result of talc.

PATHOLOGY AND PATHOGENESIS

Talc powder is a hydrous magnesium silicate and contains 82.7 per cent talc, 8.7 per cent calcium carbonate, 7.6 per cent magnesium carbonate, and 1 per cent moisture.⁷ Miller *et al*¹² in 1934 found that quartz, which is 99 plus per cent silica, when introduced into the peritoneum produced nodules that progressively increased in size. This was apparently due to chemical irritation supplied by the solution of silicate in the tissue. Particles below 10 microns in size are particularly harmful to tissues. Talc produces a pseudo-tuberculous, non-caseating, granulomatous type of lesion which previously has been described in pathologic specimens merely as chronic granuloma or chronic foreign body reactions. Lichtman *et al*⁹ point out that "material bleached out of the talc crystals is not the same as the parent substance as the degree of hydration of this derivative substance determines its toxicity." The talc crystals are not inert particles. They immobilize the phagocytes without destroying them, and therefore are not carried into the lymph stream. Usually a circumscribed granuloma is produced at the original site of contamination. Microscopically it is a fibrous granuloma with foreign body giant cell reaction. Under polarized light the smallest talc particles can be seen to be frequently engulfed by large histiocytes, whereas around the larger particles there are typical multinucleated foreign body giant cells.

The role of talc in the actual production of adhesions is a point over which there is marked difference of opinion. From their experimental work, Lichtman *et al*^{9, 10} concluded that simple inoculation of talc with little infection and trauma produced nodules rather than dense fibrosis. This point is interesting inasmuch as German⁵ states that talc alone does not cause adhesions, that trauma is necessary to produce fibrin and the talc is incorporated in the adhesions and plays a secondary role. Owen¹³ also found that talc injected intraperitoneally in rabbits produced a granulomatous lesion but no adhesions. On the



other hand Lee and Lehman⁸ state that when dry talcum powder is dusted over the serosal surfaces without trauma, massive dense uncountable adhesions are produced. It is further interesting to note that as far back as 1934, Bethune¹ described a technic for the deliberate production of pleural adhesions as a preliminary to lobectomy by the use of pleural poudrage with talc. In retrospect it is odd that surgeons using talc therapeutically to produce adhesions did not realize that they were also powdering their gloves with the same substance for operations in which adhesions were not desirable.

Apparently there is extreme variability in the individual reaction to talc. This is seen clinically inasmuch as some wounds with talc fail to heal, or break down within a few weeks following initial healing. In other cases, a period of years may elapse between inoculation with talc and the production of symptoms. The longest time interval between talc contamination and treatment in any of our cases was nine years. Others have reported granulomata developing in scars as long as 36 years after inoculation with talc (Lichtman^{9, 10}).

The presence of a talc granuloma does not necessarily presuppose a previous surgical procedure. Cases of dacrocystitis caused by talc have been reported in personnel working in surgical supply rooms where dust counts are extremely high. In one of Geiman's cases⁵ the causative agent (silica) was introduced into the tissues when the patient suffered a scalp wound while mountain climbing. Furthermore, granulomatous lesions of the rectum and vagina also may occur after the prolonged use of suppositories coated with talc.

Our own cases, however, all occurred following previous surgery, either at this hospital or elsewhere. The talc crystals may have been deposited into the wound by particles settling from the air—especially inasmuch as we do not have a separate room in which the doctors may “gown and glove”—this being done in the operating room proper. In most cases obviously the source of talc is from the surgeon's glove, both from the outside of the glove as well as following perforation. In a study by Weed and Groves¹⁹ it was observed that in a series of 4,589 operative procedures there was a perforation of one or more gloves in 74.4 per cent of the operations and that 22.6 per cent of the gloves that were used were perforated. Also, the talc may be introduced into the wound on cotton packs and sponges as well as on rubber drains. At this hospital rubber drains were formerly liberally powdered with talc for autoclaving and it is believed that this procedure is carried out in most hospitals throughout the country. Swingle¹⁸ states that regardless of how thoroughly the drains are washed, subsequent examination under the polarizing microscope still reveals birefringent crystals clinging to the rubber.

ANALYSIS OF MATERIAL

Talc crystals were identified by examination under a polarizing microscope. They are seen to be doubly refractile, varying in size up to 10 microns, and of irregular configuration. A positive statement cannot always be made whether or not a given granulomatous lesion is due to talc alone. Although talc can be found in many specimens, it may be merely contributory or incidental and

not necessarily the primary etiologic factor in the production of the granuloma. It was considered significant only when it produced tissue reaction characterized by phagocytosis of the talc crystals by histiocytes and giant cells and by the presence of fibrosis and tubercle formation. Other double refracting substances which must be distinguished from talc include hair, lint, suture material, cholesterol crystals, vegetable fibers, cotton fibers, *et cetera*.

With the above mentioned criteria in mind, a general review was made of 1,912 consecutive surgical specimens submitted to the pathologic laboratory. A total of 33 specimens containing talc granuloma was found. Eight of these were in recurrent pilonidal sinuses, there having been 21 recurrent pilonidal sinuses in the entire series. The remaining 25 specimens (from 21 patients) had been previously identified as nonspecific inflammatory granulomas.

CLASSIFICATION OF CASES

Talc granuloma was found in 33 specimens obtained from 29 patients (Table I). A breakdown of these cases is as follows:

I Chronic Granulomas as Draining Sinuses—Chest Cases—9

- a Seven of the granulomas were from five patients with pulmonary tuberculosis, the lesions being a draining sinus tract or chronic granulomatous lesion at the site of a thoracoplasty or a thoracotomy wound, and in one case at the site of a phreniclasia wound. In none of these sections could tuberculosis be found.
- b There were two non-tuberculous chest cases:
 - (1) One case was a wound granuloma and sinus tract following thoracotomy for empyema from a ruptured amebic abscess of the liver. Four revisions of the wound were required before healing finally occurred.
 - (2) One case developed a broncho-pleural fistula following a thoracotomy for post-pneumonic empyema.

II Chronic Draining Sinuses and/or Fistulae—Non-Chest Cases—9

- a Four draining sinuses of the lumbar region all found in second or later operations following an initial operation for (1) shell fragment wound, (2) nephrectomy for tuberculous kidney, (3) lumbar sympathectomy, (4) osteomyelitis of the sacrum.
- b Two fecal fistulae following appendectomy for perforated gangrenous appendices. One of these healed on excision of the sinus tract and repair of the bowel, and the other fistula persisted for four months until the patient died.
- c One pararectal sinus, operated upon five times—(three times at this hospital) before healing finally occurred.
- d One rectal fistula which had been draining since initial surgery two years previously. This patient had pulmonary tuberculosis but no tuberculosis of the rectal lesion was demonstrated on the microscopic section.
- e One case of intestinal obstruction and fecal fistula which caused death of the patient and was directly attributable to talc.¹⁸

III Inflammatory Masses—3

- a A tumor of the jaw which had progressively enlarged since the patient received initial treatment for gunshot wound of the mandible five years previously.
- b A tumor mass of the right spermatic cord which had developed following hemorrhaphy three months previously (Hematoma was also a factor).
- c Talc granuloma superimposed on an angioma which had been partially removed at the initial operation three years previously.

IV Non-Union of Radius—1

*V Chronic Cholecystitis and Malfunction of Cholecystoduodenostomy —1**VI Recurrent Cases of Pilonidal Sinuses —8*

Cases described above under I b (2), IV, and V (cases number 6, 16 and 20 respectively in Table I), and the group of cases under VI are deserving of special mention

Case 6—*Broncho-pleural Fistula with Talc Granuloma*

The patient was a 52-year-old white male who entered the hospital April 29, 1947, complaining of cough and dyspnea. Symptoms had developed a few weeks following right lower lobe pneumonia. A diagnosis of empyema was made on the basis of physical and X-ray findings and on April 30, 1947, a thoracotomy and open drainage from the empyema cavity was done by Dr. Wilson Weisel, Consultant in Thoracic Surgery. The empyema was extensive with total collapse of the lung. Three large rubber drains were inserted into the thoracotomy wound for drainage. Following this the patient developed a broncho-pleural fistula and a "frozen" lung. On August 12, 1947, decortication was done to permit free motion of the lung, a considerable portion of the pleura and scar and granulation tissue being removed. The involved bronchus was closed with interrupted sutures of 000 black silk and the wound was closed using a muscle flap to fill the cavity defect. The fistula remained closed and the wound healed well. The surgical specimen consisted of pleura and granulation tissue removed from the region of the involved bronchus. The removed tissue microscopically showed a marked proliferation of fibrous tissue with groups of lymphocytes, plasma cells and eosinophilic cells, with occasional foreign body giant cells which were seen engulfing small refractile crystals which were birefringent with the polarizing lens.

Case 16—*Non-Union of Fracture of Right Radius with Talc Granuloma*

The patient was a 23-year-old white male who sustained a simple fracture of the right radius September 28, 1946. An attempted closed reduction was unsuccessful and therefore an open reduction was performed on October 3, 1946, by Dr. P. Collopy, Consultant in Orthopedic Surgery, with insertion of a metal plate and screws. The operative wound healed well, and the patient was discharged with his arm in a plaster cast. When he returned to the Out-Patient Department nine weeks after surgery for follow-up treatment, it was found that the wound had partially broken down and there was a moderate amount of granulation tissue and a seropurulent exudate at the wound site. X-ray at that time reported "only minimal new bone formation at the fracture site." The wound failed to heal under conservative treatment which included a regime of penicillin and sulfadiazine. On March 4, 1947, five months after the initial operation, the plate, screws and fibrous tissue from the site of non-union were removed, and the fragments were immobilized by means of Kirschner wires and a plaster cast. The surgical specimen showed fragments of bone encased in fibrous tissue. In addition there was an inflammatory infiltrate and an amorphous crystalline double refractory material, identical with talc crystals, enclosed in giant cells. The wound healed by first intention and three weeks later the patient was again operated, at which time a bone graft was applied to the site of non-union. An intermedullary as well as an onlay graft was used in order to correct a one-inch defect of the radius. The wound healed postoperatively without complication.

Case 20—*Cholecystitis, and Non-Functioning Cholecystoduodenostomy with Talc Granuloma*

This patient was a 45-year-old white male who entered the hospital July 13, 1946, because of an incisional hernia at the site of a previous laparotomy for gallbladder disease. He gave a history of having had a cholecystoduodenostomy in 1937, and an exploratory laparotomy in 1945 because of persistent biliary tract symptoms. At the time of his second operation (done in an overseas army hospital) the surgeon noted a contracted gallbladder and a greatly distended common duct which was explored and drained. No stones were present, and there was no apparent blockage of the common duct. The reason for the original cholecystoduodenostomy is unknown. On admission to this hospital it was

TABLE I—Summary of Talc Granuloma Cases

Case No	Initial Diagnosis	Initial Operation	Complication— Reoperated For	Operation	Pathologic Lesion	No Times No Initial Spec- Lesion mens Re-Sub- operated mitted	Results
1	Tuberculous Empyema	Thoracotomy	Persistent drainage from operative wound	Revision of Wound	Talc granuloma in ex- cised tissue	1 1	Healed
2	Pulmonary Tubercu- losis	Thoracoplasty	Persistent drainage from operative wound	Revision of Wound	Talc granuloma in ex- cised tissue	2 2	Continued granulation— needs further revision
3	Pulmonary Tubercu- losis	Thoracotomy, Thoracoplasty	Persistent drainage from operative wound	Revision of Wound	Talc granuloma in ex- cised tissue	2 2	Healed
4	Pulmonary Tubercu- losis	Thoracoplasty	Persistent drainage from operative wound	Revis on of Wound	Talc granuloma in ex- cised tissue	2 1	Healed
5	Pulmonary Tubercu- losis	Phreniclasia	Granuloma of operative wound	Excision of granuloma	Talc granuloma in ex- cised tissue	1 1	Healed
6	Empyema (Post <i>Pneumonic</i>)	Thoracotomy	Broncho - pleural fistula Persistent drainage from operative wound	Decortication and Clos- ure Broncho pleural Fis- tula	Talc granuloma in ex- cised tissue	1 1	Healed
7	Empyema (following ruptured Amebic Abscess)	Thoracotomy	Wound breakdown with chronic drainage from op- erative wound	Revision of Wound	Talc granuloma in ex- cised tissue	4 1	Healed
8	Rectal Fistula	Excision of Fistula	Failure to heal and con- tinued drainage of fistula	Excision of Fistula	Talc granuloma in ex- cised fistulous tract	1 1	Healed
9	Para-rectal Sinus	Incision and Drainage	Continued drainage from sinus.	Excision of sinus	Talc granuloma in ex- cised sinus	4 2	Healed
10	Ruptured Appendix	Appendectomy	Fecal Fistula	Biopsy of fistulous tract	Talc granuloma in ex- cised fistulous tract	1 1	Fistula failed to heal (Died)

TABLE I—Summary of Talc Granuloma Cases

Case No	Initial Diagnosis	Initial Operation	Complication— Reoperated For	Operation	Pathologic Lesion	No Times No Initial Spec- imens Re- operated	Sub- mitted	Results
11	Ruptured Appendix	Appendectomy	Fecal Fistula	Excision of fistula and closure of bowel	Talc granuloma in excised fistulous tract	1	1	Healed
12	Shell fragment wound	Debridement of wound and secondary closure	Chronic draining lumbar sinus	Excision of sinus	Talc granuloma in excised sinus	1	1	Healed
13	Tuberculosis of kidney	Nephrectomy	Chronic draining lumbar sinus	Excision of sinus	Talc granuloma in excised sinus	1	1	Healed
14	Peripheral Vascular Disease	Lumbar Sympathectomy	Chronic draining lumbar sinus	Excision of sinus	Talc granuloma in excised sinus	3	2	Failed to heal after 7 months (Died of intestinal carcinoma)
15	Osteomyelitis of sacrum with draining sinus of left flank	Curettement of sacrum sequestrectomy and excision of sinus	Chronic draining lumbar sinus	Excision of sinus	Granulation tissue in excised sinus tract	3	1	Failed to heal
16	Fracture Right Radius	Open Reduction and Plating	Non union right radius	Removal of plate and curettement Bone graft	Fibrous talc granuloma at site of non union	2	1	Healed
17	Gunshot wound of mandible	Surgical treatment gunshot wound	Tumor mass of mandible	Excision of tumor	Fibrous talc granuloma	1	1	Cured
18	Angioma right index finger	Partial removal of angioma	Progressing tumor mass right index finger	Excision of tumor mass	Fibrous talc granuloma	1	1	Healed well
19	Right Inguinal Hernia	Herniorrhaphy	Tumor mass right groin	Excision of tumor	Talc granuloma and organized hematoma	1	1	Cured
20	Gall Bladder Disease	Cholecysto duodenostomy	Chronic Cholangitis	Common duct drainage Cholecystectomy	Chronic talc granuloma at site of Cholecysto duodenal anastomosis	1	1	Healed (Symptoms alleviated)

TABLE I—*Summary of Talc Granuloma Cases*

Case No	Initial Diagnosis	Initial Operation	Complication— Reoperated For	Operation	Pathologic Lesion	No Times No		Results
						Initial Lesion	Specimens Submitted	
21	Carcinoma of Bowel	Exploratory Laparotomy and resection of tumor	Intestinal Obstruction and Fecal Fistula	Repeated Laparotomies for intestinal obstruction and fecal fistula	Talc granuloma of excised gangrenous bowel	14	1	Wound never healed (Patient died)
22	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	1	1	Healed
23	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	1	1	Healed
24	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	10	1	Wound granulating and still not quite healed at discharge
25	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	3	1	Wound broke down and finally healed slowly by granulation
26	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	3	1	Healed
27	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	3	1	Wound granulating and still not completely healed at discharge
28	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	1	1	Healed
29	Pilonidal Sinus	Excision of sinus	Recurrent Pilonidal Sinus	Excision of sinus	Talc granuloma in excised tissue	1	1	Healed
						71	33	Total

noted that he had an icteric tinge to his skin and the icterus index was 22. The preoperative diagnosis at this hospital was chronic cholangitis based on the history of recurrent bouts of jaundice, chills and fever following cholecystoduodenostomy. Laparotomy was performed on July 30, 1946, by Dr. F. Raine, Senior Consultant in Surgery. Since cholecystogram revealed patency of the common duct, the anastomosis from the duodenum was taken down and the gall bladder was removed. Postoperatively, the patient had a stormy course with exacerbations and remissions of his cholangitis, but succeeding attacks

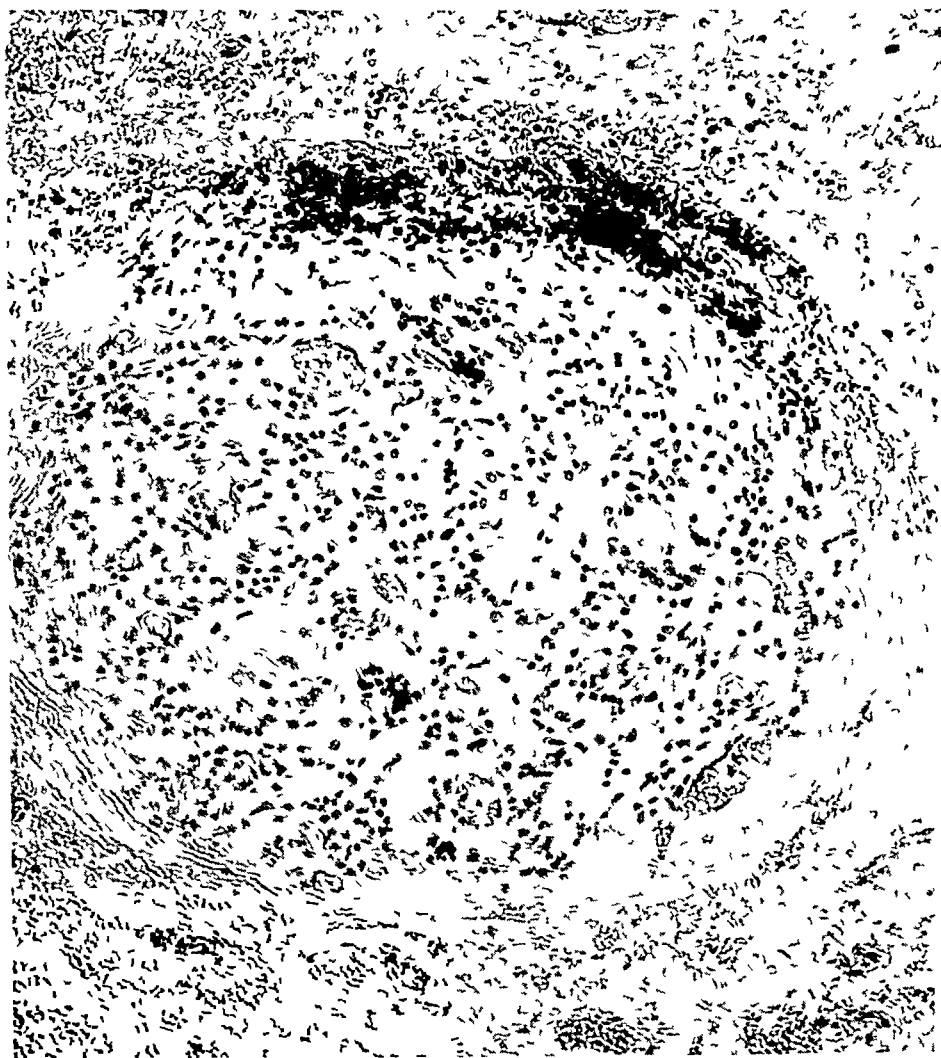


FIG. 1A—(Case 20) Cholecystitis showing talc granuloma in wall of gallbladder at site of duodenal anastomosis (low power field)

were decreasingly severe and his icterus index gradually returned to normal. The microscopic examination of the gallbladder showed the mucosa to be normal but the wall showed round cell infiltration in the submucosal area and within the muscularis a large area was found to be surrounded by fibrous tissue, in which there were epithelioid cells and giant cells, some of which engulfed foreign particles which were identified under the polarizing microscope as talc crystals (Fig. 1a and 1b).

Talc Granuloma in Recurrent Pilonidal Sinuses. A special study was made of pilonidal sinuses. Since they are notably prone to recur, the thought was

entertained that talc might be responsible for these recurrences. There was a total 58 pilonidal specimens, of which 37 were primary and 21 were recurrent. Talc crystals were not found in any of the primary cases. In eight (38 per cent) of the 21 recurrent cases, talc was found. However, in all recurrent cases, remnants of epithelial cyst or sinus could be demonstrated. Thus it could be established that talc was not the primary cause for recurrence of a pilonidal sinus. The possibility that the talc crystals acted as an irritant to the lesion causing symptoms necessitating another operation cannot be excluded.



FIG 1B — (Case 20) Same as 1A under polarized light, showing talc crystals within macrophages and giant cells (low power field)

DISCUSSION

From our study, no support can be given for or against the previously mentioned dispute as to whether talc alone is innocuous without associated trauma. A large per cent of talc granulomata were found in thoracic (thoracoplasty and thoracotomy) cases. There were 12 specimens from thoracic cases in this series which had been diagnosed previously as non-specific inflammatory granulomas. Nine of these were found to be talc granulomas. The multiple stage procedures employed and the use of drains and frequent dressings

required in these cases afford repeated trauma as well as increased opportunity for talc implantation

We believe that Case 6 is the first case of talc granuloma in a broncho-pleural fistula to be recorded. Intraabdominal fistulae due to talcum powder have been repeatedly reported, and this has also been observed in experimental animals^{9, 10}. In our case it cannot be stated how much of the responsibility talc must bear as the cause of the fistula, but at least it is a contributing factor to prevention of spontaneous closure of the sinus.

In the case of non-union of the radius (Case 16), it cannot be proved that talc alone was the cause of non-union. However, this was a clean case of elective surgery. The operative wound was healed at the time the patient was discharged. It subsequently broke down and continued to drain and would not respond to conservative therapy. This clinical picture of wound breakdown after primary healing, with the formation of a draining sinus that failed to heal on the usual regime of heat, rest, elevation, and antibiotics, is characteristic of talc granuloma. In addition, the microscopic evidence of typical talc granuloma in the fibrous tissue from the site of non-union indicates that talc in this case was the cause of non-union. The fact that primary healing rapidly occurred subsequent to the removal of the plate and fibrous tissue containing the talc, plus the fact that there is no other reasonable explanation for the failure of healing after initial plating, adds strength to the argument for talc as the etiologic agent here. We have found no previous reported case of non-union of a fracture due to interference of healing by talc.

In the case of gallbladder disease (Case 20), the introduction of talc into the wound at the time of initial surgery resulted in prolonged morbidity of the patient. The cause for the patient's original operation is not known. Nevertheless there was interference with function of the cholecystoduodenostomy as is evidenced by the observation of the surgeon at the time of the second operation for choledochotomy and drainage. He noted that the common duct was greatly distended and that the gallbladder was markedly contracted and apparently not functioning as a channel for the transport of bile to the duodenum. The talc in this case was not merely covered over with serosal cells so as to produce nodules on the peritoneal surface, as is usually the case, but was actually found in the wall of the gallbladder in the submucosal area and within the muscularis. The crystals undoubtedly were placed there when the cholecystoduodenostomy was performed. We feel justified in thus assuming that the gallbladder disease was due to talc. This was, in fact, a talc cholecystitis. We have found no similar case recorded in the literature.

There is a marked difference of opinion as to the incidence of talc granuloma. Fienberg⁴ in 1937 reported two cases and stated that in a review of 30,000 specimens he had found a total of but five cases. Saxen and Tuovinen¹⁶ in 1947 also report a low incidence, having found but six cases in 5,241 specimens. German⁵ on the other hand, as mentioned above, reported 50 cases of talc granuloma, and stated that serial sections through the omentum of patients undergoing abdominal surgery for the second time would almost always contain talc. We found 33 cases of talc granuloma in a consecutive series of 1,912

surgical specimens This would indicate that 17 per cent of the consecutive surgical procedures that were done were necessitated entirely or in part by talc. Actually, however, the figure is probably even higher than this, since a great number of wound granulomas and sinuses that are excised, many of which may contain talc, never reach the pathological laboratory. As an example, one patient had a chronic draining sinus excised on four different occasions and only one specimen was sent to the pathological laboratory, this specimen being a talc lesion. It is interesting to note (Table I) that of the 29 patients from whom these 33 specimens were obtained, 16 patients had one re-operation of the talc lesion concerned, whereas 13 patients (44.8 per cent) were reoperated two or more times, one patient having ten and another fourteen re-operations. Theoretically the talc could have been inserted into the wound at the time of the initial surgery or at any of the subsequent operations prior to the last one. It is further significant to note that these 29 patients underwent a total of 71 operations subsequent to their 29 initial procedures.

CONCLUSIONS

1 In a series of 1,912 routine consecutive surgical specimens, talc granuloma was found in 33.

2 Of the consecutive surgical procedures from which the above specimens were obtained, 17 per cent of the operations performed were necessitated in whole or in part by talc.

3 Draining sinuses following chest surgery were found to be frequently complicated by talc granuloma. In specimens from nine out of the twelve chest cases examined, talc was considered to be a major factor in the production and persistence of these sinuses.

4 To the reported cases of talc granuloma, one each of broncho-pleural fistula, failure of function of a cholecystoduodenostomy, and non-union of a fracture of the radius, is added.

5 In eight of 21 cases (38 per cent) of recurrent pilonidal sinuses, talc reaction was noted. Since in each case residuals of the sinus tract could be demonstrated, recurrence of the sinus could not be primarily attributed to talc. The talc may, however, act as an irritant necessitating revision.

6 Excision of the granuloma with the talc with resultant healing of the wound was accomplished in 21 out of the 29 cases of talc granuloma.

7 The inadvisability of the use of talc as a dusting powder is again emphasized.

Note Photomicrographs were kindly prepared by Mr. Leo Massopust of Marquette University School of Medicine.

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COMPLICATIONS OF GASTRO-INTESTINAL INTUBATION*

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GASTRO-INTESTINAL INTUBATION is one of the most important of the non-operative procedures available for the hospital care of patients. There is hardly any portion of the alimentary tract that has not been aspirated, deflated, fed or treated by rubber tubes. That such extensive threading of tubes through 32 feet of undulating, flexible, twisting intestine has encountered so few accidents is even more phenomenal than the occasional interesting account of such mishaps. Case reports of accidents resulting from gastro-intestinal intubation have been intermittently creeping into the literature. Some are merely medical curiosities, others have recorded tragedy for patients. Although the subject merits a collective review, it is believed that no article devoted exclusively to the complications of gastro-intestinal intubation has been previously published.

It is emphasized at the outset that disturbances in fluid and electrolyte balance induced by the indiscriminate use of gastro-intestinal suction are by far the most frequent and dangerous complications. One has only to measure the 24-hour volume and chloride content of secretions aspirated by a stomach tube to appreciate how quickly dehydration, hypochloremia and alkalosis may develop in a patient in whom these substances are not replaced. This physiologic phase of the subject has been amply covered by others as have the indications and contraindications of gastro-intestinal intubation. This paper is devoted entirely to the less discussed complications due to the mechanical presence of tubes in the intestinal tract.

Four case reports from the author's personal observation are submitted. The first two are knotting respectively of a Levine and Miller-Abbott tube in the stomach, the third a fatal hemorrhage from prolonged contact of a Miller-Abbott tube with esophageal varices, and the fourth a perforation of a gastric carcinoma from an indwelling Levine tube.

The complications of gastro-intestinal intubation may be classified as follows:

I SINUSITIS AND OTITIS MEDIA

An indwelling rubber tube of long standing in the nasal passage can create an inflammatory response of the nasal mucous membrane. Sinusitis then develops from infection coupled with improper drainage of the sinuses. For similar reasons otitis media is a not infrequent complication of indwelling nasal tubes in children. Apparently of no serious import judging from lack of emphasis in the literature, these complications are mentioned more for sake of completeness. It is obvious, however, that it is undesirable to use indwelling nasal tubes in patients with head colds or acute sinusitis.

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II. ESOPHAGEAL STRICTURE

Pathologists frequently observe inflammatory reaction and erosions at autopsy in the esophagus of subjects who were submitted to prolonged gastric intubation before death. Vinson¹ reports three cases of benign cicatricial stricture of the esophagus in patients submitted to continuous intubation for periods varying from two to four weeks. All responded favorably to repeated esophageal dilatations. Vinson cites this as a new cause for esophageal stricture which may crop up in the future and for which investigation should be made in patients having dysphagia following prolonged gastric intubation.

III. LARYNGEAL OBSTRUCTION

This is perhaps the most feared and insidious complication of gastrointestinal intubation. One cannot read the case reports without forever after being on the alert for the premonitory symptoms. Nineteen case reports are available of laryngeal obstruction caused by the presence of intubating tubes in the esophagus. Of these, 15 required tracheotomy and four died. The ages of these patients varied from five to 62 years. The Miller-Abbott, Levine, and Jute tubes were implicated.

The lessons to learn from the ten case reports of Iglauer & Molt² are that the obstructions can be insidious or rapid and that invariably they occur days after the tubes have been removed. In their series tubes remained in the stomach from 6 to 20 days, the average being 8½ days. Tracheotomies were performed from 5 to 30 days following removal of tubes from the esophagus. In one of the three cases reported by Holinger and Loeb,³ a tracheotomy was required seven weeks after the withdrawal of a Levine tube which had been in place only four days. At the time of publication of their article all but one of the tracheotomies performed by Iglauer & Molt were permanent. Others reporting cases of laryngeal obstruction are Wangenstein⁴ (two cases), Kaufman *et al*,⁵ Mahon,⁶ Hippenmeier,⁷ and Soubin *et al*.⁸ (each one case).

The essential findings in these cases were those of pressure necrosis of the esophagus near its attachment to the body of the cricoid cartilage. At this point the thin wall of the esophagus affords very little cushion between the mucous membrane and the cartilage. Perichondritis and ulceration of the mucous membrane of the adjacent cricoid cartilage follows with consequent acute subglottic stenosis of the larynx.

The warning symptoms of impending laryngeal obstruction in these cases are dyspnea, dysphagia, hoarseness, blood streak sputum, and croupy cough. The onset of dyspnea is an ominous sign, for this develops gradually over a period of days. Less frequently does dyspnea develop rapidly before tracheotomy is required. Kaufman *et al* recommend daily mirror inspection of the larynx for inflammation or edema and withdrawal of the tube if the patient develops dysphagia or hoarseness.

IV. KNOTTING OF THE TUBE

Many radiologists have observed potential knotting of a tube in the stomach, but in its withdrawal the knot is usually disentangled. Removal from

the stomach via the esophagus of a knotted tube doubtless has occurred more than the reports would indicate. The reports of Billings,⁹ Boles,¹⁰ Niles,¹¹ Golob,¹² Paviot & Levrat,¹³ Fiancenco,¹⁴ and Martini *et al*¹⁵ make a collection of seven cases of knotting of tubes. Each reports a case of knotting of a metal tipped Rehbus type tube in the procedure of biliary drainage. All but one of these tubes knotted in the stomach and in each case the incident was attributed to gastric hypermotility.

In the case of Billings a Rehbus tube was passed without incident for proposed biliary drainage. After waiting 30 minutes for passage into the duodenum, the patient suddenly became dyspneic and attempted to remove the tube herself, but encountered difficulty passing the cardiac orifice. By having the patient swallow water her physician was able to draw the tube past the cardiac orifice and slowly by resistant jerky efforts to bring it up the esophagus. Two separate single knots were present starting one inch from the metal tip. With the exception of Paviot & Levrat's case all tubes knotted in the stomach and were withdrawn in a similar resistant jerky manner without any apparent after ill-effect on the patient.

The most unusual report is that of Paviot and Levrat from France. At 9 00 P M a nearly new metal tipped Einhorn tube was passed for biliary drainage without incident on a 37-year-old male having cholelithiasis. During the night 80 cc of bile had drained from the duodenum. The next morning after giving atropine and magnesium sulfate the patient became nauseated and attempted emesis. Only 10 cm of the tube could be withdrawn and this was apparently from stretching of the rubber in an otherwise immovable tube. Radiologic examination disclosed a double complex knot of the tube in the duodenum caught against the pyloric sphincter. Atropine and bromides failed to permit withdrawal. The following day the tube was divided with scissors as far down the pharynx as possible. Forty-eight hours later the entire tube along with the double knot measuring 3 x 5 cms passed spontaneously at the anus. These authors attributed this accident to the prolonged presence of the tube in the duodenum. Whether the tube might not have tied itself in the stomach and then passed through the pyloric sphincter is not mentioned.

Two additional instances of knotting of tubes within the stomach are given from the author's experience while surgical resident at the Episcopal Hospital in Philadelphia.

Case 1—W J, 38-year-old colored male had an ileocolostomy and exteriorization of a gangrenous irreducible ileocecal intussusception on November 17, 1947. Postoperatively a Levine tube was passed. It remained in place 5 days and was then withdrawn because of ineffective drainage. The interne was surprised to find the tube tightly tied in a single knot one inch from its tip.

Case 2—J S, male, age 56, had symptoms of intermittent large bowel obstruction of 5 days duration. On December 1, 1947, a Miller-Abbott tube was passed at 9 00 P M. The following morning after drainage of 240 cc of gastric contents, the patient passed flatus and a formed stool. It was decided to remove the tube and give barium by mouth. The clamp on the balloon side of the tube was removed in the routine manner. The

patient asked to withdraw the tube himself and in so doing encountered considerable jerky resistance After moderate effort the tube and knot came out the nose (Fig 1) Four inches from its tip the tube was tied in a single loop knot The balloon was empty and



FIG 1—Photograph of Miller-Abbott tube knotted 4 inches from its tip
It was withdrawn by a patient after being in his stomach 12 hours

unruptured which suggested that the knot must have been tightly drawn at the time of removal of the tube and just after the escape of air from the balloon The patient had no ill effects from the incident

V RUPTURE OF ESOPHAGEAL VARICES

Schindler¹⁶ lists esophageal varices among the absolute contraindications for gastroscopy, fearing hemorrhage from its use. It would seem that for parallel reasons esophagogastric intubation would be contraindicated in any patient with cirrhosis of the liver suspected of having esophageal varices. A review of the Index Medicus since 1912 has failed to unearth a single article or case report devoted to rupture of esophageal varix from a tube lying in the esophagus. The following case report should therefore be interesting, if indeed, this is the first such case report.

Case 3—H. S., 63-year-old male was admitted to the medical service of Episcopal Hospital, Philadelphia, on January 22, 1947, with acute onset of knife like precordial pain of 15 minutes duration, orthopnea, and abdominal distention allegedly of 4 days duration. He was a known alcoholic. His cardiac failure responded well to digitalization. The abdomen was distended but not tender and presented a shifting dullness. Radiologic survey of the abdomen revealed distention of the stomach and small intestine. Some confusion existed as to the cause of the patient's abdominal distention. Believing there existed a combination of ascites and intestinal obstruction the resident passed a Levine tube into the stomach for continuous suction. On January 23rd a Miller-Abbott tube was passed and on January 24th radiologic examination disclosed its tip well into the small intestine with considerable diminution in the distention. After the removal of 4 liters of serous fluid with specific gravity of 1.012 by paracentesis abdominis, the liver edge was readily palpated at the level of the navel. It was firm and coarsely nodular. The Miller-Abbott tube remained in place to prevent recurrence of intestinal distention. On January 29th, after 7 days of intubation, he vomited about a liter of bright red blood followed by the passage of bloody stool a few hours later. In spite of repeated transfusions and other supportive measures, the patient died of exsanguination on January 31st, 36 hours after the onset of hemorrhage.

At autopsy about 3 liters of straw colored fluid was free in the peritoneal cavity. The liver weighed 1850 Gm, was studded on its surface with brown nodules as great as 2.5 cms in diameter. This nodularity continued throughout the parenchyma as circumscribed tumor masses, some of which were soft and others almost cystic or necrotic. Very little normal liver tissue could be demonstrated. The spleen weighed 240 Gm. The entire gastro-intestinal tract was filled with clotted fresh blood. No obstruction was present. The esophagus was grossly inflamed and presented numerous varicosities of the distal third. There was frank ulceration and necrosis of the mucosa overlying at least 2 of these veins. It appeared that this had been the source of the bleeding.

Histologic examination of the liver tumor performed by the Department of Pathology at Temple University Hospital confirmed the impression that this was a primary hepatoma superimposed on a long standing cirrhosis of the liver. Microscopic sections of the esophagus (Fig. 2 and 3) demonstrated varicosities with deep ulceration of the mucous membrane.

COMMENT While it cannot be proved that this hemorrhage from esophageal varices might not have occurred spontaneously without the presence of an indwelling tube, the knowledge that a Miller-Abbott tube was in contact for six days with varices of the esophagus and the demonstration of esophagitis and ulceration at autopsy appear to bear more than coincidental relationship to the hemorrhage.

VI RUPTURED VISCUS

It is a surgical principle to obviate pressure necrosis and perforation of such structures as blood vessels, mesentery and serosa of gut by studiously avoiding prolonged contact of these structures with hard rubber drains and tubes. Analogous to this it might be implied that similar precaution should be exercised in regard to intestinal intubation, at least with respect to diseased gut. A wealth of experience with intubation under all circumstances had shown little cause for concern until the revealing papers of Mahon,⁶ Eliason and Welty,¹⁷ Berger and Achs,¹⁸ and Holinger and Loeb.³ These cases are here abstracted



FIG 2



FIG 3

FIG 2 —Photomicrograph of esophagus of Case 3, showing stratified squamous epithelium undergoing necrosis with invasion by lymphocytes and neutrophils $\times 100$

FIG 3 —Photomicrograph of esophagus of Case 3. This shows greatly dilated and blood-filled veins in the submucosa of a patient with esophageal varices $\times 100$

along with an additional one by the author to serve as a warning that perforated gut can occur from the presence of intubating tubes. That each case is different suggests the wide possibilities of this accident.

The first case report of ruptured stomach attributed to the presence of an intubating gastric tube is that of Mahon. A female had 18 inches of gangrenous ileum resected with end-to-side anastomosis of ileum to ascending colon. A Levine tube was passed into the stomach for aspiration and remained in place nine days. Two days following removal of the tube she suddenly developed laryngeal obstruction necessitating a tracheotomy. Death occurred in 10 hours. At autopsy massive atelectasis of two lobes of the lung secondary to complete inflammatory occlusion of the larynx was seen along with four areas of necrosis

on the anterior wall of the stomach just above the greater curvature. Perforation of the stomach had occurred through two of these areas presumably by pressure necrosis. The cause of death was due to peritonitis and massive atelectasis.

The second in this series is a case report by Eliason and Welty suggesting the possibility of perforated esophagus from intubation. Their 44-year-old female patient was intubated by a Levine tube for 36 hours following a resection of strangulated small bowel. The tube was then removed because of respiratory distress. Repeated vomiting of coffee ground material followed removal of the tube. At autopsy a rupture of the anterior wall of the distal end of the esophagus was found. The adjacent mediastinal tissues were deeply stained with partially digested blood. These authors mention that the role which the Levine tube may have played is uncertain. A third and similar case was reported by Holinger and Loeb. Their 57-year-old female patient eviscerated eight days after a gastroenterostomy for extensive carcinomatosis. Because the "stomach tube" was poorly tolerated by the patient it was removed and repeatedly reinserted during a period of 11 days. A final overzealous attempt to insert it resulted in a perforation of the esophagus with death from a mediastinal abscess.

The fourth in this series is the case reported by Berger and Achs. A 40-year-old female was admitted with small intestinal obstruction caused by an adhesion band at the ileum. Because the patient refused operation, a Miller-Abbott tube was passed. It migrated to the ileum to a point where it would not proceed further in spite of the fact that it was repeatedly withdrawn to the 18-inch mark over a period of 12 days. On the tenth day of intubation there was no drainage from the tube. On the 12th day of intubation a celiotomy disclosed the metal tip of the Miller-Abbott tube protruding through a perforation in the ileum just proximal to the obstructing band. The balloon was unruptured. The patient made an uneventful recovery after division of the band and closure of the perforation. This accident was attributed to pressure necrosis of a dilated, thin walled, and obstructed intestine caused by prolonged contact with the metal tip. The authors believed this to be the first report of rupture of small intestine from intubation.

The fifth in this series is case 4 reported by the author.

Case 4—A G, No 8067, male, age 56, admitted to Hamot Hospital, Erie, Penna., on October 19, 1946, having been referred by Dr. Harold Ghering, of Edinboro, Pa. The patient had a two-weeks history of marked weight loss, anorexia, and vomiting. Physical examination was essentially negative aside from presence of marked cachexia. Peritoneoscopy performed on October 21st disclosed pyloric carcinoma with liver metastasis. Because of obstructive symptoms a gastroenterostomy was decided upon. The patient's stomach was prepared for two days with continuous Levine tube suction and gentle lavage with normal saline solution. On October 23rd Dr. Orel Chaffee performed a celiotomy through a left para-median incision. The tumor previously visualized by peritoneoscopy was found encircling the distal third of the stomach, Fig. 4. On the anterior surface of the stomach through the midst of the tumor there was a perforation about 8 mm in diameter through which the tip of a Levine tube was just protruding into the peri-

toneal cavity. A plastic exudate encircled the perforation. There was almost no fluid in the peritoneal cavity and very little inflammatory reaction. The stomach which had been frequently flushed and continuously aspirated for 48 hours in preparation for gastric surgery was now clean, empty, and of normal size. The tube was withdrawn 4 inches by the anesthetist and the perforation in the tumor closed by a purse string suture of No. 0 chromic catgut. An anterior gastroenterostomy was then performed. The patient made an uneventful recovery and at the time of hospital discharge on November 7th had gained 5 pounds and was able to ingest a soft diet without distress. According to Doctor Ghering his condition continued at home unchanged until November 30, 1946, when he died suddenly of a coronary infarction.

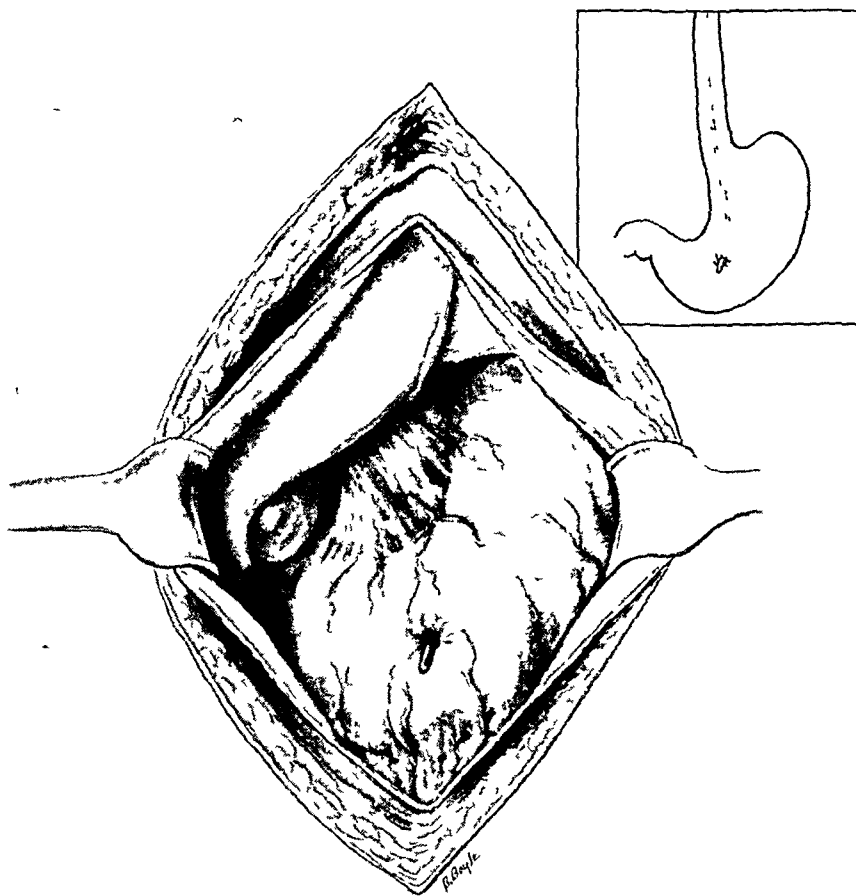


FIG 4—Case 4. Artist's concept of Levine tube perforating stomach at area of carcinomatous degeneration. Inset at right is a schematic drawing of the tube in relation to the stomach.

COMMENT. Here again the perforation is attributed to pressure necrosis of the stomach by an inlying tube. In this case it occurred in only two days of intubation because this was a carcinomatous stomach. A rule to grow out of these experiences is the following: "Make sure that the tip of the tube changes its position in relation to the gut daily." This can best be done by having the patient either swallow more tubing or withdraw a portion each day.

Bisgard and Overmiller¹⁹ collected 217 reported cases of spontaneous rupture of the stomach. Glassman²⁰ in his classical review of spontaneous perforation of the stomach warns that very slight trauma may cause perforation of a diseased stomach wall. Strassman²¹ and Key²² have each reported a case of spontaneous rupture of the stomach during gastric lavage. These mishaps were doubtless due to the volume or force of fluid used in the diseased stomach and not to the presence of a tube. As such they would be classified along with the remarkable case reports of Lemmon and Paschal²³ and Murdfield²⁴. In their patients the stomachs ruptured after being filled with large quantities of beer or other fluids followed by ingestion of sodium bicarbonate.

VII INABILITY TO WITHDRAW THE BALLOON TIPPED TUBE

It is entirely possible that a situation could exist where the balloon of a Miller-Abbott tube could not be deflated. Patency of the air channel of the tube and free communication with the balloon should be determined daily. This may be done by aspirating all air out of the balloon after removing the clamp on the air outlet tube. In a dry syringe, about 15 to 20 cc of air may then be injected into the balloon. If there is a free communication of the air channel the plunger will be forced back into the syringe by the elasticity of the balloon. If there is doubt about whether the balloon is deflated or any resistance encountered in withdrawing the tube, one should never forcibly pull on the tube. A roentgenogram will immediately determine whether or not the balloon is collapsed.

Wangensteen²⁵ cites the case of an hour glass deformity of the balloon occurring at the ileocecal junction. The tube could not be withdrawn nor could the portion of the balloon beyond the ileocecal sphincter be deflated. Finally the balloon spontaneously ruptured permitting withdrawal. A tentative diagnosis of stricture at the terminal ileum was not substantiated at exploration.

Allen and Welch²⁶ state that they have had Miller-Abbott tubes descend to the lower small intestine and then found that the balloon did not deflate. Their suggestion for handling this complication is to perform an early laparotomy and to puncture the balloon through the intestinal wall with a needle.

Harris and Gordon²⁷ in writing about their mercury filled balloon cite one experience where the balloon could not be withdrawn after it had passed beyond the ileocecal valve. Persistent attempts to pull the bag through the valve resulted in a tear of the bowel with formation of a localized abscess. They now advise cutting the tube at the nares if the bag passes beyond the ileocecal valve. The entire tube then is eliminated spontaneously at the anus. In their seven experiences of this sort the time taken for the tube to appear at the anus varied from 24 hours to 10 days. Attempts to obviate this with the Harris tube have now been made by reducing the length so that only four feet of the tube can pass into the intestine. They further stress that the position of the tube be determined by radiologic examination after it has passed the 3-foot mark.

VIII BREAKAGE OF MERCURY FILLED BAG

Breakage of a mercury filled bag in the intestine has occurred to almost everyone who extensively uses the Harris or Cantor tube. No ill effects have been reported from this phenomenon.

SUMMARY

1. An attempt has been made to review all of the reported complications of gastro-intestinal intubation since the first one recorded in 1924. The total number is not great in proportion to the widespread use of intubation.

2. The following headings are the complications discussed:

- I Sinusitis and Otitis Media
- II Esophageal Stricture
- III Laryngeal Obstruction
- IV Knotting of the Tube
- V Rupture of Esophageal Varix
- VI Ruptured Viscus including esophagus, stomach, and small bowel
- VII Inability to withdraw Balloon Tipped Tube
- VIII Breakage of Mercury Filled Bag

3. Four original case reports are presented of knotting of the tube, perforation of a cancerous stomach, and rupture of esophageal varices.

4. Warning notes are sounded to avoid complications with gastrointestinal intubation as follows:

- a) Remove tube if the patient presents a dyspnea, dysphagia, hoarseness, blood streak sputum, or croupy cough.
- b) Position of the tip of the tube should be changed daily.
- c) Nasal intubation should be avoided in patients with sinusitis and head colds.
- d) The presence of esophageal varices is a contraindication to gastric intubation.
- e) Remove the tube as soon as it has completed its mission.
- f) Tubes with mercury bag should be followed by roentgen ray after the 3-foot mark has been reached to prevent them from passing beyond the ileocecal valve. In the event the bag passes the ileocecal valve, it must not be withdrawn, but rather permitted to pass spontaneously by anus.

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INADVERTENT GASTRO-ILEOSTOMY*

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FORTUNATELY, the surgical error of anastomosing the stomach to the ileum instead of to the jejunum is uncommon. Twenty-seven cases of gastro-ileostomy have been found recorded in the literature. The first was reported in 1915 by Martin and Carroll¹. Mercur² in 1917 reported another and mentioned a case seen by Judd in 1912. A fourth was mentioned by Klein³ in 1926. These last two cases were not reported in detail and are excluded. Nine cases were added by Rivers and Wilbur,⁴ three by Kogut and Stein,⁵ eight by Smith and Rivers,⁶ three by Brown, Colvert and Brush,⁷ and one by Bailey and Castleton.⁸ Two others are excluded (Rivers and Wilbur) because they were actually gastrojejunostomies with jejuno-ileostomies, although the clinical syndromes produced were similar.

An interesting and constant feature about the reported instances of gastro-ileostomy is that the original operation was performed by some surgeon other than the one reporting the case. This might imply that many such cases are never reported and that this condition is not as rare as a review of the literature would indicate.

Twenty-two of the 24 cases previously reported in sufficient detail to include in this study were patients on whom a gastro-enterostomy was being done for peptic ulcer. In only two reported instances has this condition been associated with a partial gastrectomy. One of these was reported by Kogut and Stein⁵ and the other by Smith and Rivers.⁶ The case reported herewith is the third reported instance in which a partial gastric resection was done with an anastomosis between the stomach and the ileum. Of the three cases with gastro-ileostomy following partial or subtotal gastric resection, two were done for duodenal ulcer and one for carcinoma of the antrum of the stomach.

A brief summary of the reported cases of gastro-ileostomy is presented in Table I.

It is felt that the occurrence of a gastro-ileostomy following gastric resection is sufficiently rare to justify another report. Of particular interest in this case is the associated malrotation of the midgut, which was a large factor in causing this surgical error. None of the previously reported cases had such an associated condition to explain why the ileum was mistaken for the jejunum.

CASE REPORT

Miss N. P. Hosp. No. 16-314, a 38-year-old white nurse, was admitted to Salt Lake General Hospital on December 7, 1947, with complaints of diarrhea, severe weight loss and increasing weakness of 18 months' duration.

* Submitted for publication, February, 1949.

TABLE I—*Summary of Reported Cases of Inadvertent Gastro-Ileostomy*

Reported by	Age and Sex of Patient	Original Diagnosis and Operation	Duration of Gastro-ileostomy Before Reconstructive Surgery	Weight Loss Since Gastro-ileostomy in Pounds	Reconstructive Procedure	Result
1 Martin and Carroll 1915	26 F	Gastric ulcer Gastro-ileostomy	12 mos	Yes, but amount not stated	Reconstruction of normal pathway	Good
2 Mercur 1917	38 F	?Duodenal ulcer Gastro-ileostomy	3 yrs	Yes, but amount not stated	Reconstruction of normal pathway	Good
3 Rivers and Wilbur 1932	35 F	Duodenal ulcer Gastro-ileostomy	6 mos	25	Partial gastrectomy with reconstruction	Good
4 Rivers and Wilbur 1932	44 M	Gastric ulcer Gastro-ileostomy with jejuno-ileostomy	4 yrs	18	Reconstruction of normal pathway	Good
5 Rivers and Wilbur 1932	39 M	Gastric ulcer Gastro-ileostomy	20 mos	45	Reconstruction of normal pathway	Good
6 Rivers and Wilbur 1932	44 F	?Duodenal ulcer Gastro ileostomy	17 mos	Not stated	Reconstruction with gastro duodenostomy (plastic)	Good
7 Rivers and Wilbur 1932	31 M	Duodenal ulcer Gastro-ileostomy	14 mos	50	Reconstruction of normal pathway	Unknown
8 Rivers and Wilbur 1932	43 F	?Duodenal ulcer Gastro-ileostomy	13 mos	Not stated	Reconstruction of normal pathway	Good
9 Rivers and Wilbur 1932	35 F	?Duodenal ulcer Gastro-ileostomy	25 yrs	30	Reconstruction of normal pathway	Good
10 Kogut and Stein	27 M	Duodenal ulcer Gastro ileostomy	1 yr	Not stated	Reconstruction after excising ulcers of stomach and ileum at anastomosis	Recurrent ulcer Post gastro enterostomy done later
11 Kogut and Stein	26 M	Duodenal ulcer Gastro-ileostomy	2 yrs	Yes, great but number of pounds not stated	Partial gastrectomy	Good
12 Kogut and Stein	63 M	Ca of stomach Partial gastrectomy	No reconstructive surgery	Not stated	None	Died several days postoperatively
13 Smith and Rivers 1943	35 F	?Duodenal ulcer Gastro-ileostomy	6 mos	25	Reconstruction	Good
14 Smith and Rivers 1943	53 F	Duodenal ulcer Gastro ileostomy	9 mos	36	Reconstruction and P G J	Good
15 Smith and Rivers 1943	37 M	Duodenal ulcer Gastro-ileostomy	3 yrs	6 pounds in preceding 4 weeks	Reconstruction and pyloroplasty	Pain recurred

TABLE I — (Continued)

Reported by	Age and Sex of Patient	Original Diagnosis and Operation	Duration of Gastro ileostomy Before Reconstructive Surgery	Weight Loss Since Gastro-ileostomy in Pounds	Reconstructive Procedure	Result
16 Smith and Rivers 1943	56 M	Duodenal ulcer Gastro ileostomy	8 yrs	36	Reconstruction and pyloroplasty with temporary feeding jejunostomy and cholecystectomy	Good
17 Smith and Rivers 1943	61 M	?Duodenal ulcer Gastro ileostomy	3 mos	60	Reconstruction with gastro jejunostomy	Good
18 Smith and Rivers 1943	53 M	Duodenal ulcer Gastro ileostomy	23 yrs	Yes (7 pounds in 3 months preceding)	Reconstruction	Good
19 Smith and Rivers 1943	34 M	Duodenal ulcer Gastro ileostomy	2 yrs	5	Partial gastrectomy	Good
20 Smith and Rivers 1943	58 M	Duodenal ulcer Partial gastrectomy with gastro ileostomy	6 mos	60	Reconstruction	Good
21 Brown Colvert and Brush 1947	62 F	Duodenal ulcer Gastro ileostomy	4 yrs	28	Reconstruction	Good
22 Brown Colvert and Brush 1947	39 M	Duodenal ulcer Gastro ileostomy	2 yrs	20	Partial gastrectomy	Good
23 Brown Colvert and Brush 1947	64 M	Duodenal ulcer Gastro ileostomy	7 yrs	44	Not stated	Good
24 Bailey and Castleton (in press)	72 M	Duodenal ulcer Gastro-ileostomy	2 yrs	30	Reconstruction of normal pathway	Good
25 Moretz	38 F	Duodenal ulcer Subtotal gastrectomy with gastro ileostomy	18 mos	101	Reconstruction after block resection of anastomosis	Good

Ten years prior to her admission, she had first noted occasional severe epigastric pain. This was not related to meals but was relieved by milk or cream and antacids. These pains became more frequent and more severe and later were relieved by eating.

Seven years before her admission, she had had an episode of fairly massive hemorrhage after an attack of severe epigastric pain associated with the passage of 10 tarry stools and weakness. Shortly thereafter an exploratory laparotomy was carried out by a competent surgeon. An anomaly was noted in the duodenal region. The duodenum extended straight downward into the jejunum without going behind the superior mesenteric vessels or becoming retroperitoneal. The lower part of the second and third portions of the duodenum had a well-developed mesentery from two to three inches long. A duodenal ulcer was demonstrated and "the ulcer-bearing area was inverted."

Following this operation she continued on a strict medical regimen with exacerbation of her symptoms when the diet was relaxed or when there was added emotional strain. She had occasional bouts of increased pain associated with tarry stools in 1945 and 1946.

While she was attending college she noted increased pain and tarry stools with each examination week

In July, 1946, a subtotal gastrectomy was carried out by the same surgeon. He noted the presence of many dense adhesions throughout the abdomen and it was only after much difficult dissection that he was able to liberate the stomach and pylorus sufficiently to allow resection of approximately two-thirds of the stomach. There were so many adhesions present that it was not possible to trace the small bowel back to the duodenum or the ileocecal valve for positive identification. A loop of small intestine lying in the left upper quadrant was used in constructing the gastro-enterostomy.

The postoperative course was satisfactory except that on her third postoperative day a severe diarrhea developed which never entirely ceased. The number of defecations per day varied from two to twenty. The stools were frequently bulky with very foul odor and occasionally frothy. Undigested food particles were occasionally seen in the stool 45 minutes after being ingested. She progressively lost weight and strength in spite of added vitamins and liver injections. No abdominal pain similar to that experienced prior to surgery occurred. There were occasional "gas pains" and frequent crampy pains for a few minutes after the passage of feces. During the six months prior to her admission here, she was bedridden. Her weight had decreased from 191 pounds prior to gastrectomy to 100 pounds on her present admission to the Salt Lake General Hospital. Food intake had continued to be adequate for a normal person. There was occasional vomiting or eructation of fecal character.

Her past history was irrelevant except for (1) an appendectomy in 1920, complicated by disruption of the right-rectus incision (the wound was resutured and the patient was discharged after one month of hospitalization), and (2) small-bowel obstruction in 1936 requiring laparotomy with release of adhesions (no further significant difficulty with obstructive symptoms occurred).

Examination revealed a markedly emaciated, tall, intelligent woman who lay quietly in bed. She rolled her head from one side to the other on request but was barely able to lift her head from the pillow. She could hardly lift her knees from the bed and was unable to lift either entire lower extremity. Her temperature was 98.6 F, pulse 76, respiration 20, blood pressure 85/65, height 5 feet 9½ inches, weight 100 pounds.

Except for the extreme emaciation, abnormal physical findings were scarce. Her skin was loose and pale. Her tongue was bright red, with enlarged papillae. There were three well-healed abdominal incisions: one in the lower midline, one in right rectus and one in left upper rectus. No solid organs or masses were palpable within the abdomen. Very slight tenderness was present in the left lower quadrant.

Slight edema was present in the left lower extremity chiefly at the ankle and upper thigh. Her marked generalized muscular weakness was compatible with her extreme emaciation.

Laboratory Findings

Blood Red blood cells 4.17 million, hemoglobin 12.5 gm, hematocrit 38, icterus index 5, uncorrected sedimentation rate 20, MCV 91, MCH 30, white blood cells 5,050 with differential of 48/P, 40/L, 5/E, 5/M, 2/juveniles, blood chemistry BUN 9.5, sugar 83, carbon dioxide 58, P₁ Cl 600, total protein 4.0 (albumin 2.0, globulin 2.0), calcium 9.2, phosphorus 4.8, alkaline phosphorus 3.2 B U, uric acid 4.6.

Stool Guaiac negative. Soft yellow with undigested food but without abnormal particles of fat, no parasites, 17.6 per cent of feces were solids, 11.2 per cent of feces were total lipids, 2.54 per cent of feces were fatty acids, 63.6 per cent of solids were total lipids, 14.4 per cent of solids were fatty acids, 22.7 per cent of total lipids were fatty acids.

Urine Pale yellow—specific gravity 1.010, Ph 6, sugar 0, albumin 0. Microscopic normal.

Gastric analysis revealed no free acid in the fasting specimen or after histamine
There were seven units of total acid in the fasting specimen and 20 units
30 minutes after histamine

Intravenous Glucose Tolerance Test (0.5 mg/Kg as 20 per cent solution
intravenously over 30")

F B S	57
30"	181
60"	109
90"	100
150"	60

Oral Glucose Tolerance Test 100 Gm—orally

F B S	70
30"	60
60"	75
90"	120
150"	80
210"	74

Course in Hospital The patient was admitted to the Medical Service, where the diagnostic work-up was carried out and extensive supportive treatment given. A barium enema revealed the cecum and the ascending colon to lie on the left side of the abdomen just to the right of the descending colon (Fig 1). No connection between the stomach and the colon was visible. The first gastro-intestinal series demonstrated a patent gastro-enterostomy, the pattern of the small bowel suggesting ileum rather than jejunum. There was a rapid filling of the colon, which suggested the possibility of a gastrojejuno-colic fistula. Re-examination, however, revealed that the anastomosis was between the stomach and the distal third of the ileum, without a connection with the large bowel. The terminal ileum was dilated moderately and exhibited both peristaltic and antiperistaltic waves (Fig 2). Within two hours after the ingestion of barium, it was observed in the cecum.

A high-caloric, high-protein diet was tried, but no gain in weight or strength resulted. The patient was tried on a 4,500-calory diet containing 200 grams of protein, 110 grams fat, and 678 grams of carbohydrate. This she could not tolerate and an exacerbation of the diarrhea occurred. She continued to lose weight until she weighed only 90 pounds. Multiple blood transfusions and intravenous plasma and protein hydrolysates were given with some improvement in blood protein (total protein 4.5 with albumin 2.1 and globulin 2.4) and body weight (97 pounds).

It was felt that the patient would require jejunostomy feeding before she could be built up enough to stand a major operation. Therefore, under local anesthesia, on December 27, 1947, a Witzel type of jejunostomy was performed. There was relative freedom from adhesions and it became obvious at this time that there was a developmental anomaly of the gastro-intestinal tract with faulty rotation of the midgut. After some exploring, the duodenum was traced distally and a jejunostomy was performed at a point approximately 15 inches from the duodenojejunal junction. The abdominal opening was made in the left middle quadrant in an effort to have it out of the way of the gastric surgery to be performed subsequently.

The patient stood this procedure well and was started the same day on a special formula† of predigested food, 30 cc per hour. This formula consists of amino acids, dextromaltose, cream, salt mixture, vitamins and water in such a proportion that 1 cc contains about 1 calory. These feedings were tolerated quite well and were increased

† The formula used was essentially the same as described by Hollander, Rosenak and Colp.⁹

FIG 1



FIG 2A



FIG 2B

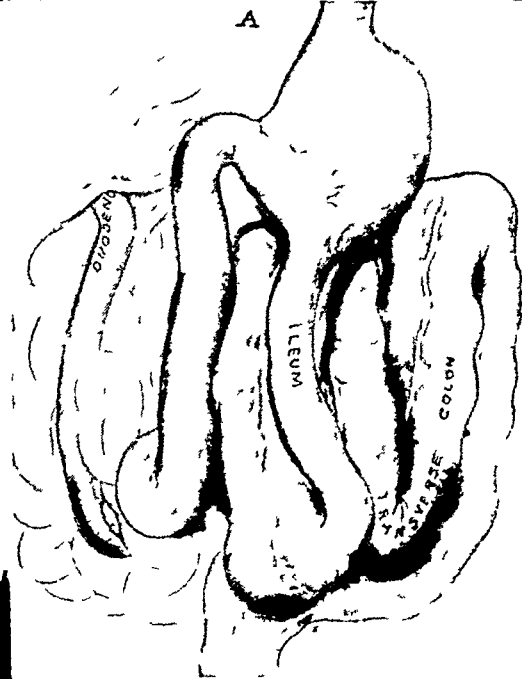


FIG 3

FIG 1—This barium enema revealed practically the entire large bowel to be situated in the left half of the abdominal cavity. There was no reflux of barium into the stomach, indicating that a gastrocolic fistula probably did not exist.

FIG 2—A gastro-intestinal series demonstrated the flow of barium into the colon within two hours. The small-bowel pattern suggests ileum. The limb of ileum labeled "A" represents the proximal limb, which is considerably dilated and in which both peristaltic and reverse peristaltic waves were seen on fluoroscopy. The distal limb "B" is also moderately dilated.

FIG 3—This drawing illustrates the congenital malrotation of the midgut and the gastro-ileostomy as found at operation. Note that the duodenum does not cross over the abdomen beneath the superior mesenteric vessels but continues downward in the right side into the jejunum, most of the jejunum being located in the right lower quadrant. Most of the large bowel is located in the left half of the abdomen. The gastro-ileostomy had been constructed at a point about 14 inches from the ileocecal valve. Both the afferent and the efferent limbs of ileum are considerably dilated.

soon to 150 cc per hour. The patient complained of frequent abdominal cramps and had occasional nausea and vomiting but not enough to necessitate discontinuance. Occasional exacerbation of the diarrhea also occurred. In general, she progressed quite satisfactorily and on January 20, 1948, her total proteins were 6.9 Gm with 5.5 Gm albumin and 1.4 Gm globulin. She had gained in weight to 104 pounds. Her improvement continued, and before further surgery was carried out, her weight was 111 pounds, total protein 6.6 and A/G ratio of 2:1.

She was up in a chair four days after the jejunostomy but she could not walk because of muscular weakness. She walked unassisted about three weeks after the jejunostomy, for the first time in seven months.

On February 12, 1948, under cyclopropane anesthesia, exploration was carried out. The anomaly of rotation was confirmed. The gastro-ileostomy was resected, removing the distal inch of remaining stomach and the attached ileum. An end-to-end aseptic anastomosis was made between the two ends of ileum using a single row of Halsted sutures of No. 60 cotton. A gastrojejunostomy was then formed, anastomosing the jejunum at a point about eight inches proximal to the feeding jejunostomy to the distal end of the remaining stomach.

Gross and microscopic examination of the resected specimen showed evidence of mild chronic inflammation of the stomach and the ileum in the region of the anastomosis. There was no area of erosion or ulceration.

Her postoperative course was uneventful. Jejunostomy feedings were continued for 12 days after the operation and then discontinued since her oral intake had become adequate. On February 29, 1948, she was discharged from the hospital weighing 117 pounds, having normal bowel movements and feeling very well.

She was seen about two months after her discharge, on April 21, 1948, at which time her serum proteins were normal and her weight had increased to 141 pounds. There was still slight ankle edema, thought to be related to old thrombophlebitis of deep thigh and pelvic veins. There had been occasional loose bowel movements on some mornings. The drainage from the old jejunostomy had practically ceased. When last seen, 10 months after operation, she was completely asymptomatic and the jejunostomy had closed.

DIAGNOSIS

Diagnosis should not be too difficult in most cases. The signs and symptoms in this case are typical. There was onset of diarrhea three days after the construction of the gastro-ileostomy, which might well have aroused suspicion of the error that had been made. The persistence of this diarrhea with marked loss of weight and strength would support such a suspicion. The absence of abdominal pain other than some crampy pain after defecating is somewhat unusual. Vomiting was not a prominent feature although it was occasionally present.

Brown and others summarized the signs and symptoms of the cases reported prior to 1947 and found that 17 of 24 complained of abdominal pain, 14 of 24 had diarrhea and 13 of 24 had some vomiting. Of 20 patients with statements regarding weight loss, 19 had lost weight. Fecal vomiting and hemorrhage had occurred in a few patients and six had developed ulcers in the ileum at the site of anastomosis. The signs and symptoms have also been discussed by Bailey and Castleton,⁸ who summarized in table form all previously reported cases.

The rapid filling of the colon after swallowing barium was practically

diagnostic in this case. The lack of reflux into the stomach of barium given as a barium enema was evidence against a gastrocolic fistula.

Brown and others pointed out that serial barium-meal films of the gastrointestinal tract frequently show some refilling of the stomach after it had emptied. This was demonstrated from three and one-half to five and one-half hours after the barium meal by the reappearance of barium in the stomach from the ileum. This finding depends upon the flow of barium through the pylorus into the small bowel and on through the small bowel until it re-enters the stomach through the gastro-ileostomy. Therefore, it could apply only to those cases in which there had been a gastro-ileostomy performed without gastric resection. It also could not apply to those cases in which the pyloric obstruction is complete.

Baigen and Rankin¹⁰ in 1930 cited 12 patients who had developed severe postoperative diarrhea due to ulcerative colitis. These symptoms began from 3 to 15 days after abdominal surgery, chiefly on the stomach or biliary system. This condition can usually be differentiated from a gastro-ileostomy by barium enema.

Gastro-ileostomy alone is less serious than when accompanied by a gastric resection. With gastrectomy, the duodenum, the jejunum and the proximal ileum are completely by-passed and the only appreciable food absorption is from the stomach and the terminal ileum. Without gastric resection, a part, depending on the degree of pyloric obstruction and the patency of the gastro-ileostomy stoma, of the food goes through the entire small bowel. Therefore, relatively few symptoms result from gastro-ileostomy when the major part of the food goes through the pylorus, as in several reported cases of many years' duration (one case of 23 years' duration reported by Smith and Rivers). Other cases with practically complete pyloric obstruction have the same rapid downhill course as those patients with gastric resection, such as one case reported by Smith and Rivers of three months' duration and a weight loss of 60 pounds.

The development of ileitis or ulceration of the ileum has been discussed by Rivers and Wilbur⁴ and by Kogut and Stein.⁵ This case had no ulceration and showed only mild chronic inflammation of the stomach and the ileum near the anastomosis.

PREVENTION

Most cases of gastro-ileostomy are probably associated with inexperienced surgeons. A few such errors may have resulted from the surgeon's failure to realize the importance of using the jejunum instead of the ileum for a gastro-enterostomy. Most, however, are probably the result of difficulty in differentiating between a loop of jejunum and a loop of ileum. The appearance of a single loop of small intestine may not be sufficiently characteristic of either jejunum or ileum to permit positive identification. Much more certain is the practice of identifying a loop of small bowel not by its appearance alone but by its relationship to known landmarks. The most useful landmark in choosing a loop of jejunum for gastro-enterostomy is the ligament of Treitz.

In the absence of the ligament of Treitz, as in the case reported here, an anomaly of rotation should be suspected and a loop should be selected by tracing the duodenum distally or by tracing the small bowel proximally from the cecum. The presence of many adhesions complicates the problem.

Although a loop of bowel picked up in the left upper quadrant beneath the transverse mesocolon will usually be jejunum, it must be identified with certainty before it is used in a gastro-enterostomy.

Dott¹¹ has beautifully described the embryologic changes in the intestinal tract and has pointed out many of the more frequent errors in rotation. McIntosh and Donovan¹² have discussed the clinical significance of faulty rotation and have given case histories illustrating these features.

The faulty development in this case is illustrated in Figure 3. This anomaly represents a derangement of the second stage of rotation, consisting of nonrotation of the midgut loop. This form of derangement is not uncommon and has been described by Dott¹¹. Incomplete rotation of the midgut prevented the duodenum from becoming posterior to the superior mesenteric vessels, instead the duodenum coursed downward in the right side of the abdomen to the duodeno-jejunal junction and most of the jejunum remained in the right lower quadrant. Most of the small bowel on the left side of the abdomen was ileum ending in the ileocecal valve situated low in the midline. The cecum and ascending colon had not rotated in front of the superior mesenteric vessels but had come to rest chiefly to the left of the midline.

McIntosh and Donovan¹² reported one case with an anomaly practically identical with that present in this patient. Dott explained this anomaly as a result of the umbilical orifice being so large that it exerts no restraining influence on the return of the cecum through this orifice. This enlarged umbilical orifice allows the cecum to return to the abdominal cavity along with or before part of the small bowel, thus eliminating the factor which normally causes a rotation of the midgut.

In this case the malrotation caused the loops of ileum to be located in the left upper quadrant and the extensive adhesions prevented thorough exploration, thus accounting for the surgical error.

PREOPERATIVE TREATMENT

Many of these patients have lost much weight. Brown and others⁷ stated that of the 20 cases reported in which there was a statement regarding weight loss, 19 had lost weight. Many are in poor nutritional state and a few are in a critical condition. Increased food intake with high protein and carbohydrate content is routinely given to these patients. Enriched formula feedings have been used and massive vitamin intake has been assured. However, food taken by mouth is very poorly assimilated and these measures seldom materially improve the patient's condition when the proximal bowel is excluded, as in gastro-ileostomies with partial gastrectomy. A good guide to the progress being made is afforded by following the patient's weight and serum proteins.

In seriously ill and markedly emaciated patients, intravenous feedings are necessary. Infusions of whole blood, plasma and amino acids may be of marked benefit. In this patient all these measures were tried but no material improvement could be obtained. Such a case provides an ideal indication for a feeding jejunostomy. Figure 4 illustrates the relationship of the jejunum, the ileum and the stomach after jejunostomy in this patient. A synthetic aliment similar to that described by Hollander, Rosenak and Colp⁹ was used, beginning a few hours after jejunostomy, with marked success. The patient's weight and serum protein increased rapidly with reversal to normal of the A/G

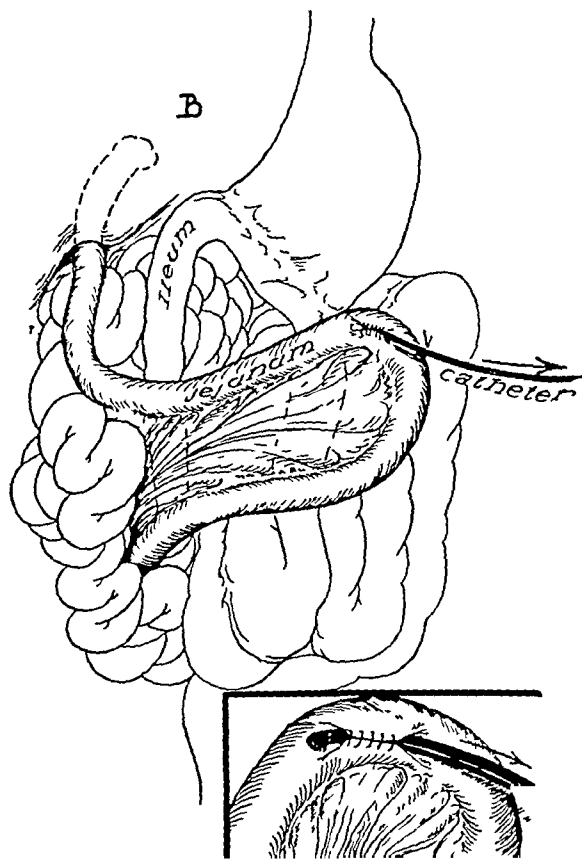


FIG 4

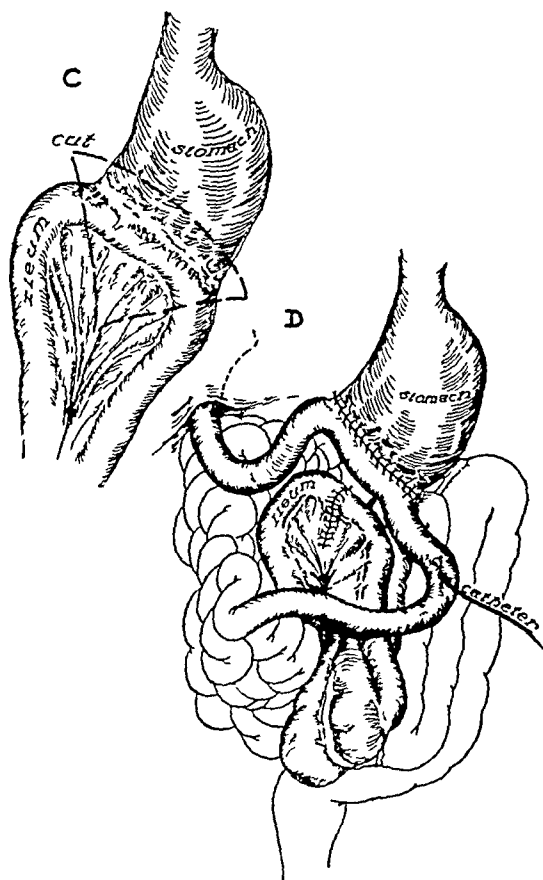


FIG 5

FIG 4—A Witzel jejunostomy was performed at a point about 15 inches from the duodenojejunal junction. The abdominal opening was made well on the left side of the abdomen so that it would not interfere with the contemplated reconstructive surgery.

FIG 5—In the upper figure the broken lines indicate the limits of resection. After excising this area, an end-to-end anastomosis was made between the two ends of ileum. A gastrojejunostomy was completed to the jejunum at a point about 8 inches proximal to the jejunostomy, the lower figure shows the relationship between the gastrojejunostomy, the jejunostomy and the ileum when completed.

ratio. Within three weeks she was able to walk unassisted for the first time in seven months. It is very dubious that this patient could have survived the major operation of reconstructing a gastrojejunostomy without first having the benefit of a feeding jejunostomy.

In none of the previously reported patients has a feeding jejunostomy been done as a preliminary to the major reconstruction. In one case reported by

Smith and Rivers a temporary jejunostomy was done at the time of the reconstruction. Most of the previous reports stressed the importance of preoperative treatment, but very seldom was any estimate given as to how successful the preoperative measures had been. There were no observations on weight gain prior to operation and few observations on change in serum protein prior to operation.

A wise procedure would be to employ a feeding jejunostomy in those patients who are in poor nutritional status and who do not respond satisfactorily to forced feedings intravenously or by mouth.

OPERATIVE TREATMENT AND RESULTS

The desired treatment depends upon the existing circumstances. If a subtotal gastrectomy has already been done, the problem is different from that when only a gastro-ileostomy has been carried out.

Gastro-ileostomies without gastrectomy will be considered first. Twenty-two of the reported cases are in this category and all these patients were suffering from peptic ulcer, the gastro-ileostomy being done to help this condition. The following chart summarizes the treatment carried out in this group.

*Operative Treatment in 22 Cases of Gastro-Ileostomy for Peptic Ulcer
(Without Coincident Gastrectomy)*

	Number of Cases	Results		
		Good	Poor	Unknown
1 Reconstruction of normal continuity	13	11	1*	1
2 Partial gastrectomy with gastrojejunostomy	4	4		
3 Reconstruction with pyloroplasty	2	1	1**	
4 Reconstruction with pyloroplasty and temporary feeding jejunostomy	1	1		
5 Reconstruction with posterior gastrojejunostomy	1	1		
6 Not stated	1	1		

* Ulcer recurred—satisfactorily treated by posterior gastro enterostomy later

** Ulcer pain recurred

No deaths occurred in this group. Recurrence of duodenal ulcer occurred in two cases, one after simple reconstruction, the other after reconstruction with pyloroplasty.

There are really two main problems in the surgical treatment of gastro-ileostomy. First, the gastro-ileostomy must be corrected, second, the patient may still have the original difficulty to be treated, namely, the duodenal ulcer.

Ideally, the preferred surgical treatment would care for both these problems at one time. Depending upon one's views on the value of vagotomy, one may choose to take down the gastro-ileostomy, close the openings in the stomach and ileum and to perform a vagotomy with a pyloroplasty or gastrojejunostomy if pyloric obstruction exists. Instead, one may prefer to carry out a subtotal gastric resection with gastrojejunostomy, after taking down the

gastro-ileostomy Either of these two procedures can be carried out if the patient is a good surgical risk If not a good risk, it still may be possible in some to take down the gastro-ileostomy and resect the vagus nerves Usually some effort to treat the ulcer should be made at the same time the gastro-ileostomy is corrected Otherwise there is a good possibility that the duodenal ulcer will give further difficulty If there is marked pyloric obstruction, some means of exit for the gastric contents must be provided It is to be noted that four cases had a subtotal gastric resection carried out with good results in each case

The operative treatment for those cases of gastro-ileostomy in which a partial gastrectomy already has been done requires only the correction of the gastro-ileostomy, since the ulcer probably requires no further treatment Of the three cases with gastric resection complicated by gastro-ileostomy, two were for ulcer and one was for carcinoma of the stomach The patient with carcinoma died 36 hours after the original operation, the gastro-ileostomy being found at autopsy The other two cases were treated by taking down the gastro-ileostomy and constructing a gastrojejunostomy The follow-up of these two cases revealed no further difficulties

One satisfactory procedure is to resect the area of anastomosis including the distal inch or so of the stomach and the ileum involved in the anastomosis between clamps An end-to-end anastomosis is then carried out between the two ends of the ileum and a Polya gastrojejunostomy is performed This block type of resection was done in this case and it is felt that this offers some advantages over disconnecting the anastomoses, closing the ileal stoma and using the original gastric stoma in the gastrojejunostomy The block resection can be done more quickly and possibly with less soiling More confidence is placed in an anastomosis between freshly cut edges than between old and fibrotic edges It is believed that there is less danger of complications such as leakage at the anastomosis or obstruction This procedure is illustrated in Figure 5

One cannot assume because of the uniformly good results in the reported cases that the reconstruction of a gastro-ileostomy is not a serious undertaking Many patients are probably reoperated upon by the same surgeon who made the original error and these are not reported It is also probable that many patients unsuccessfully operated upon for this condition are not reported If the unreported cases were reviewed, it is extremely likely that the statistical results would be considerably different

SUMMARY

A case is presented of a gastro-ileostomy following subtotal gastric resection for duodenal ulcer In the treatment of this patient, a feeding jejunostomy was first established which greatly improved the general condition of the patient Several weeks later there was a successful resection of the gastro-ileostomy and reconstruction of a gastrojejunostomy with end-to-end anastomosis between the two ends of ileum

There was an associated anomaly of rotation of the midgut which predisposed the patient to this surgical error. Absolute identification of the anatomy before performing a gastro-enterostomy is necessary.

Vigorous preoperative treatment is essential to restore these patients to good condition. A preliminary jejunostomy for feeding is of value in the severely emaciated patient who fails to respond to other measures.

A block resection of the gastro-ileostomy is advocated for those patients who have had subtotal or partial gastric resection. For those who have not had a gastric resection, satisfactory results may be obtained by taking down the gastro-ileostomy and combining this with a subtotal gastrectomy or a vagotomy.

Twenty-four instances of gastro-ileostomy have been reported previously in sufficient detail for study. Twenty-two of these were of gastro-ileostomy done without gastric resection. Only two, plus a third reported here, were gastro-ileostomies following a partial gastric resection.

It is probable that the reported instances of this type of surgical error represent only a small percentage of the actual number of such errors. The uniformly good results in the reported cases probably are not indicative of the results in the group not reported.

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Editorial . . .

THE INQUIRING MIND

ALL SURGEONS aware of their responsibility to their profession and to society must inevitably be concerned with the training of those who will succeed them. There are often two components of training. One is the imparting of technical skills or knowledge. The second consists of imparting a point of view, or philosophy, to the trainee. In the trades, the union or the employer may be equally desirous of imparting to the trainee a particular philosophy, yet it is obvious that a man can be skilled at a trade no matter what his philosophy. In other fields, the point of view is an integral part of the training, just as important as the technical skill. Thus the training of a soldier involves not only the imparting of technical skill but of imbuing the individual with an unwavering loyalty towards his country. Without this second component the technical skills are useless, or may even be harmful to the accomplishment of the desired goal—a well-trained and loyal soldier. The training of a surgeon requires the imparting of both technical knowledge and a philosophy. The latter is the more important of the two.

A knowledge of the desired objective is implicit in any training program. That part of a surgeon's life in which he fulfills the objectives of his training rarely lasts more than 30 years. Part of the training objective might be considered as teaching the technical skills which will be required by the surgeon during these 30 active years, but it is impossible to predict the surgical procedures which he will be called upon to perform. His technical training, therefore, must be largely concerned with basic skills and knowledge, rather than with particular technics which may well become obsolete. For example, mastoidectomies, and thoracotomies for empyema following pneumonia, are rarely performed now, owing to the discovery of chemical and organic materials which are effective in the control of infections. The surgeon of tomorrow may be operating in different fields. The emphasis may pass from the surgical treatment of infections to that of the correction of congenital abnormalities. The field of vascular surgery is rapidly enlarging its scope. The surgeon may soon be operating under direct vision within the heart itself. Future developments of medical science may eliminate much of the surgical treatment of conditions resulting from degenerative processes. At present the radical local extirpation of cancer by surgical means constitutes the best weapon against this condition. Enormous resources are now being made available for investigation of the cause and cure of cancer. When such research reaches fruition surgical treatment of the disease may become obsolete.

It is apparent, therefore, that the modern training of a surgeon must include the acquisition of a broad background in fundamental fields of

medical knowledge. Physiology, biochemistry, anesthesia and probably radiation and nuclear physics, all will provide a background which will help the surgeon of tomorrow to cope with the inevitable advances in medical science in the coming years. The examining boards in the surgical specialties should recognize the importance of these fields of knowledge instead of laying major emphasis on the preclinical fields of anatomy and pathology. Certainly it is just as important for the surgeon to be thoroughly acquainted with the important subjects of nutrition, fluid and electrolyte balance and the dynamics of cardiorespiratory physiology, as it is for him to know the anatomy of the region in which he is operating and the pathologic conditions which he may encounter. A knowledge of anatomy and pathology is just as essential as it was 50 years ago, but to halt there in the training of the modern surgeon is to overlook the advances of the past generation.

Of far greater importance than teaching either a fundamental background or a technical skill is the indoctrination of the surgical aspirant with a philosophy. This philosophy is that of the inquiring mind. The ability to pose pertinent questions involves intelligence and implies the ability to draw logical conclusions from the answers. It is diametrically opposite to the type of mind which unquestioningly accepts the written or spoken word of considered authorities. This unquestioning attitude has no place in the field of science. It was responsible for the long stagnation in scientific thought through the dark ages, which in the field of anatomy perpetuated the errors of the Galenic school for centuries, until Vesalius questioned these dogmas and threw new light upon anatomy and related subjects by direct observation.

None will venture to disagree that the inquiring mind is essential to scientific progress. That it is also a valuable and essential attribute of the modern practicing surgeon is less generally realized. The practice of medicine is not the simple acquisition of a set of rules which when applied to the problem posed by the particular patient will always result in the correct diagnosis or correct therapy. The patient with an ulcer of his duodenum or stomach does not always present the classical symptoms of epigastric pain between meals, relieved by the taking of food or alkali. The practicing physician or surgeon who relies upon a text-book set of rules to make a diagnosis of appendicitis will find himself frequently in error. Questioning is an integral part of the elucidation of symptoms. The correct diagnosis of disease depends upon a careful evaluation of all the available evidence. The same exercise of judgment is required in therapy as in diagnosis. Dependence upon simple rules of thumb never characterized the competent physician or surgeon.

The inquiring mind is typical of youth. It is exemplified by what are sometimes regarded as the "tiresome" questions of small children. It characterizes the attitude of intelligent students through school, college and post-graduate studies. Too often, through incompetent pedagogy, this attitude of mind is gradually stifled, with the result that a graduating student leaves the halls of learning with a set of ideas and concepts which gradually harden into an unyielding structure.

It may be doubted that it is possible to cultivate the inquiring mind in one field of knowledge without disturbing the fixed ideas and conceptions which have already been formed in other fields. Yet all of us have known outstanding leaders in the surgical profession who eagerly embrace new developments in surgery, but who may be completely lacking in this attitude of mind when it comes to politics, literature, art, etc. The inquiring mind is one which is actively engaged in the search for truth and knowledge. It is impossible for one individual to master all knowledge and it is easier to accept authority in other fields than to question it.

It is possible for the student to acquire this attitude of mind at an early stage in his professional training and to retain it throughout his active career, because with good pedagogy the questioning attitude will become an integral part of the learning process. A properly trained student will not accept unwarranted conclusions which may appear in published medical articles, but will study the text and draw his own conclusions. The poorly trained student of medicine, on the other hand, is likely to accept conclusions of this character because of the authority of the written word. It is obvious which of these men will be the better practitioner.

Why is this invaluable component of training occasionally neglected? First, the teacher of surgery may be unaware of the importance of this aspect of training, and secondly, he may discourage questions because of the unconscious fear that if he does not know the answer he will "lose face" in the eyes of his students. The importance of inculcating this attitude of mind in young surgeons will become apparent if the matter is given thoughtful consideration. The unconscious fear of betraying ignorance can be overcome if boldly stated and honestly faced.

A great deal has been written in the past generation about the training of surgeons. Much of it is concerned with where he is to be trained, and how long, and the qualifications of his instructors. Much attention has been paid to evaluating his training by examination. Too little thought has been devoted to the objectives of training. Let us be sure of our surgical goals. Because of our concern with the formal indoctrination of skills, we should not neglect an essential philosophy. The best surgeons of tomorrow, as of yesterday, will always be those with inquiring minds.

JOHN H. GIBBON, JR.

LETTER TO THE EDITOR

DEAR SIR

After reviewing this most interesting paper of Dr Clarence C Eckert, I should like to call attention to the fact that, in my opinion, it is most difficult indeed, in our present state of ignorance regarding carcinoma, to place certain cases of carcinoma of the breast in the category of "inoperable", and I must confess that I am not in agreement with Haagensen and Stout's classification, on which Doctor Eckert's paper is based

In 1929, in collaboration with Dr Dean Lewis, I published a follow-up study of almost 1,000 cases of carcinoma of the breast which had been operated upon by Doctor Halsted and Doctor Finney, Sr, together with all of their residents from 1889 to 1929, inclusive. This follow-up revealed many points of interest. The operation performed by the various operators—all Halsted-trained men—was a typical Halsted radical mastectomy, so that the operative procedure was constant. Pathologic diagnoses also were made by Dr W H Welch and his staff in the Department of Pathology, of the Johns Hopkins Hospital, so that there was no variation in the interpretation of the specimens and microscopic sections.

With this background, it was soon discovered in the follow-up that dogmatic statements in regard to prognosis following radical mastectomy for carcinoma of the breast should *not* be made, and certainly the so-called classification of inoperability by Haagensen and Stout did not hold for this series of almost 1,000 cases. The statement by the latter authors to the effect that when carcinoma of the breast develops during pregnancy or lactation it is always inoperable, is literally untrue. There were patients operated upon not only in the Johns Hopkins Hospital but at other hospitals in Baltimore, for carcinoma of the breast during pregnancy who lived for a period of years or are still living. One patient with whom I was personally connected has lived about ten years. This patient had a very malignant medullary type of carcinoma of the breast with metastasis to the axillary glands that developed midway in pregnancy. After a radical mastectomy had been performed, the ovaries and uterus containing the fetus were removed and this patient is alive and well today. There are others in this series who survived for some years and who were lost track of, but they may well be alive.

The second point, namely, that edema of the skin or nodular implantation of the growth near by the original tumor is a sign of inoperability is likewise inaccurate. There were a number of patients in this series at the Johns Hopkins Hospital in whom edema of the skin had occurred, and also subcutaneous implantation of the tumor, who were operated upon successfully and had survived for a number of years at the time of the follow-up study. One patient in particular, operated upon by Dr William Sowers while he was resident surgeon at the Johns Hopkins Hospital in 1905, a woman, was still alive 25 years after, at the age of 80 plus. This patient survived a radical mastectomy for an ulcer-

ated carcinoma of the breast that had not only ulcerated through the skin over the entire dome of the breast, resulting in a foul-smelling wound with implantations in the skin surrounding the ulceration, but also had metastasis to the axillary and supraclavicular lymph nodes. Doctor Sowers performed a very radical operation upon her, removing the breast and the underlying structures to the chest wall, dissecting the axillary nodes and at the same time going above the clavicle as was done in those days, and removing the lower cervical chain of lymph nodes, which were invaded. The operation consumed more than five hours, but the patient was cured and, as I stated above, was alive 25 years later at the age of 80 plus.

It is, of course, to be admitted that this was one case in practically one thousand, but when one is dealing with a human being and with a relatively unknown condition such as carcinoma, it seems to me that no stone should be left unturned to save the patient's life. I think few will deny that, had not Doctor Sowers performed such a radical and meticulous operation, the patient would not have survived as long as she did.

In any series of breast tumors there are patients with ulceration of the skin who have lived a number of years following radical mastectomy and have been much better off following such an operation than they would have been had the ulceration been treated palliatively, with the consequent infection and foul discharge, to say nothing of the bleeding which often occurs in those patients on whom an operation has not been performed.

I think anyone adhering to Haagensen and Stout's classification would be led astray and that a number of patients who should have radical mastectomies would probably be denied their one chance to be cured.

The five-year cures that have often been discussed is essentially misleading. The word survival should be substituted for cure. In the series studied by us at the Johns Hopkins Hospital there were recurrences in every decade, up to 33 years postoperatively in two cases.

It would seem to me that the aim of the surgeon in treating carcinoma of the breast should be not only to attempt to cure the patients of the disease process but also to prolong their lives and make them physically and mentally as comfortable as possible. If it were possible completely and minutely to examine the entire bodies of persons apparently cured of carcinoma, it might well be demonstrated that we in some manner retarded the spread of the disease by removing the original tumor and that people may die with, if not of, the residual depositions of malignant growths. The report of Peugniez, who did a partial gastrectomy for carcinoma of the stomach at the Hotel Dieu in Paris, and who, 25 years later, when the patient returned to the hospital and died of lobar pneumonia, found at autopsy some adenocarcinoma in the retroperitoneal glands which were histologically indistinguishable from the primary carcinoma is a famous case. Thus, the growth had lain latent over that period of time. It would seem, therefore, that it behooves the surgeon to perform within reason, thorough extirpation of carcinomatous growths whenever the region involved and the extent permit such procedure.

Local recurrence in the skin, in several instances in my own personal experience have been successfully treated by radical secondary excision. In the absence of distant metastases or local signs of inoperability, such as fixation due to involvement of the chest wall, brachial plexus or the great vessels, it is our belief that the great majority of patients with carcinoma of the breast should be given the opportunity of having radical mastectomies.

Another point which is not emphasized in Doctor Eckert's paper, or that of Haagensen and Stout in their classification of "categorically inoperable cases," is the prognosis depending on the histologic type of tumor. Almost everyone who has treated carcinoma of the breast knows, or should know, for instance, that a duct cell or comedocarcinoma of the breast, no matter how extensive the ulceration or edema, offers far the best prognosis of all the malignant tumors of the breast. It would, of course, be possible to have such a tumor of the breast in a late stage and still, in spite of the external appearance of inoperability, be amenable to radical surgical extirpation. These opinions are based upon many years' experience of the staff of the Johns Hopkins Hospital associated with the late Doctors Halsted, Finney, Bloodgood, Heuer, McClure, Reid, Holman and many of the resident surgeons connected with Doctor Halsted's staff who were intensely interested in the study of malignant tumors of the breast. I think that in our present state of knowledge all malignant tumors of the breast should be treated surgically and by a radical operation similar to the one proposed many years ago by Doctor Halsted and unimproved since. It transcends human knowledge, at present at least, to prognosticate accurately in such cases unless as stated before, there are distant metastases or local involvement of structures which are obvious and need no discussion. The efficacy of any other form of therapy, including deep roentgen, before or afterwards, has never been convincing to me and certainly, in my opinion, radical surgical excision is still the therapeutic method of choice.

The main difficulty with the classification "categorically inoperable" is that it is too categorical.

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BOOK REVIEWS

REVIEW OF ACUTE INTESTINAL OBSTRUCTION by Rodney Smith, Asst Surgeon, St George's Hospital, London The Williams & Wilkins Co, Baltimore, Md, 1948 Price \$5 00, 240 pages

This book presents the mechanisms of acute intestinal obstruction due to various causes and discusses the pathological physiology and its treatment The last one hundred pages are concerned with the individual varieties of acute intestinal obstruction, and because of the large number can be only briefly discussed

Emphasis is given to conservative decompression with indications for operation, with the author's opinion being that aseptic types of anastomoses are to be preferred While there is more or less complete agreement that there are types of acute intestinal obstruction which can be relieved temporarily or permanently with the use of the Miller Abbott tube alone, not all will agree with the statement that "once the balloon of the Miller Abbott tube is in the duodenum, decompression can always be achieved" While for the most part the local intraperitoneal instillation of sulfonamides has been abandoned in this country, the author believes strongly that it should be used and devotes a chapter of discussion in support There is a paucity of discussion in regard to electrolyte control and replacement, and the author cites his lack of experience with parenteral protein alimentation due to lack of supplies in England

While nothing new is presented, the book is an excellent review of the subject, recognizing the limitations of space

DAVID V HABIF, M D

PREOPERATIVE AND POSTOPERATIVE CARE OF SURGICAL PATIENTS by Hugh C Ilgenfritz, St Louis, C V Mosby Company, 1948, price \$10 00

This book contains much useful information and on the whole fairly represents the principles and methods accepted by present-day surgery The author provides a useful set of rules and procedures for actual preoperative and postoperative situations He has chapters devoted to the problems of biliary, gastric, colonic and thoracic surgery, as well as to general subjects such as wound care, surgical infections and shock

The book suffers somewhat from the author's efforts to cover too broad a range of topics His discussions of physiological chemistry and of the techniques of laboratory determinations are too abbreviated and elementary to be worthwhile The author writes in a didactic manner, and a more imaginative discussion of conflicting viewpoints of the controversial problems would have been desirable and, very likely, useful

NICHOLAS S GIMBEL, M D

BOOKS RECEIVED

MEKIE, ERIC C

Handbook of Surgery The Williams and Wilkins Co, Baltimore, Maryland, 1949

VETERANS ADMINISTRATION

Veterans Administration Technical Bulletin Series 10 Volume II, Veterans Administration, Washington, D C, 1949

CORLETTE, C E

A Surgeon's Guide to Local Anaesthesia—A Manual of Shockless Surgery The Williams and Wilkins Co, Baltimore, Maryland, 1948

KOSMAK, GRO W
RUTHERFORD, ROBERT N
Editors

Transactions of The Third American Congress on Obstetrics and Gynecology Western Journal of Surgery Publishing Co, Portland, Oregon, 1948

BOOK REVIEWS

Annals of Surgery
July 1949

MALLET-GUY, PIERRE

La Chirurgie Bihaire sous Controle Manometrique et Radiologique per Operatoire Masson et Compagnie, Paris, France, 1947

CARLING, SIR ERNEST ROCK
ROSS, J PATERSON

British Surgical Practice Hodgkin's Disease to Lymphogranuloma Volume 5 The C V Mosby Company, St Louis, Missouri, 1948

KEEFER, CHESTER SCOTT

The Uses of Pencillin and Streptomycin The University of Kansas Press, Lawrence, Kansas, 1949

ANNOUNCEMENT

THE KAPPA DELTA AWARD FOR RESEARCH IN ORTHOPEDIC SURGERY

The National Council of the Kappa Delta Sorority has inaugurated a prize of one thousand dollars to be given annually by the American Academy of Orthopaedic Surgeons for the best research in orthopedic surgery performed during the year by an individual in the United States. The first award, for the year 1949, will be announced at the seventeenth annual convention of the Academy in New York, February 11, 1950. Those wishing to compete for this prize can secure further information from Dr. Walter Stuck, 1426 Nix Professional Building, San Antonio, Texas, Chairman of the Award Committee for 1949.

EDITORIAL ADDRESS

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John H. Gibbon, Jr., M.D.

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Exchanges and Books for Review should be sent to Dr. Gibbon at the above address.

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THE MECHANISM OF THE POST-GASTRECTOMY "DUMPING" SYNDROME*

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ONE OF THE FUNCTIONS of the stomach is that of a reservoir. Normally it evacuates a mixed meal in about three to four hours at an estimated rate of about 10 to 15 cc per minute. When the gastro-intestinal tract has been deprived of its gastric reservoir, as after a gastroenterostomy or a subtotal gastric resection, the ingested food may enter the jejunum almost immediately and give rise to unpleasant symptoms, these constituting what has been called the "dumping syndrome."

The symptoms consist of any combination, or all, of the following: a feeling of warmth, sweating, tightness or pain in the epigastrium, nausea, weakness, palpitation, vertigo and even collapse. They vary in severity and in the degree to which they incapacitate the patient, but usually cause him to lie down after meals until they subside. They occur after all meals in some individuals, but only after certain ones in others. They usually make their first appearance when the patient resumes feedings postoperatively and may trouble him for weeks or years. Some patients learn that the avoidance of certain foods, or of liquid, may prevent the development of the syndrome.

The mechanism of production of the symptoms has been variously ascribed. It has been maintained¹ that the symptoms are due to hypoglycemia, which is alleged to occur secondarily to hyperglycemia, the latter resulting from rapid absorption of carbohydrate from the jejunum. It has also been held² that they are due to the hyperglycemia (hyperglycemic shock) because they occur during the hyperglycemic phase of postprandial absorption. An entirely different explanation is that the symptoms result from mechanical distention of the jejunum by the "dumping" of food into it^{3, 4, 5}. It has also been stated⁶ that there are two sets of symptoms: (1) early postprandial, due to mechanical distention of the jejunum (and possibly in some cases due to absorption of unchanged protein with the subsequent effect of shock) and (2) late postprandial, due to hypoglycemia.

In view of the above conflicting opinions as to the mechanism of the production of symptoms, a number of experiments was performed on 16

* Submitted for publication, December, 1948

patients manifesting post-subtotal gastrectomy "dumping" symptoms and on control subjects with intact stomachs. As a result, a mechanism for the development of the early postprandial symptoms has suggested itself which appears to explain the clinical and experimental observations more satisfactorily than any of the previously proposed ones.

SUBJECTS AND PROCEDURE

The subjects were patients from the Gastro-Intestinal Section of the Medical Clinic and from the surgical and medical wards of this hospital who had undergone a subtotal gastric resection (Table I). Each, except one (Case 14), had roentgen evidence of rapid passage of a barium meal from the esophagus into the jejunum.

TABLE I—*Description of Patients and "Dumping" Symptoms Manifested*

Case No	Age/ Sex	Subtotal Gastric Resection performed for	Time of Occurrence of Symptoms with Relation to Meal	Nature of "Dumping" Symptom *
1	63/M	Marginal ulcer	Immediately after	Epigastric fullness, weakness, palpitation and sweating
2	39/M	Duodenal ulcer	Immediately after	Epigastric fullness, weakness and palpitation
3	35/M	Duodenal ulcer	Immediately after	Epigastric pain, pallor, palpitation, sweating and vertigo
4	28/M	Duodenal ulcer	Immediately after	Nausea, weakness, vertigo, blurred vision and epigastric fullness
5	63/M	Duodenal ulcer	Immediately after	Epigastric fullness, weakness, vertigo and sweating
6	30/M	Duodenal ulcer	Immediately after	Nausea, weakness, pallor, sweating and palpitation
7	58/F	Gastric carcinoma	Immediately after	Nausea, weakness, palpitation, epigastric fullness and vertigo
8	40/F	Duodenal ulcer	Immediately after	Nausea, weakness, palpitation
9	63/M	Gastric ulcer	Immediately after	Weakness, palpitation and vertigo
10	26/M	Duodenal ulcer	Immediately after	Nausea, weakness, palpitation and vertigo
11	55/M	Gastric carcinoma	Immediately after	Epigastric fullness and pain, vertigo, palpitation and sweating
12	42/M	Duodenal ulcer	Immediately after	Nausea, weakness, vertigo, palpitation, vomiting and sweating
13	68/F	Leather bottle stomach	Immediately after	Epigastric fullness, nausea, vertigo, weakness, palpitation and blurring of vision
14	48/M	Duodenal ulcer	Immediately after	Epigastric fullness, sweating, weakness, vertigo, palpitation and collapse
15	47/M	Duodenal ulcer	Immediately after	Palpitation, weakness, vertigo and fainting
16	30/F	Duodenal ulcer	Immediately after	Epigastric pain, weakness, nausea and palpitation

* All patients had to lie down after a meal during period of symptoms.

The filtrate for the blood sugar determinations was prepared by the Folin-Wu method (zinc sulfate-barium hydroxide) which, in our laboratory, yields higher values (average, 253 $\frac{1}{2}$ mg per 100 cc, range, 6 to 60) than when the filtrate is prepared by the Somogyi (tungstic acid) technique. Other details of procedure are described in the sections dealing with results.

RESULTS

I *Time of Occurrence of Symptoms in Relation to Ingestion of a Meal*
Each of the 16 patients who complained of the "dumping" syndrome reported

† Figures were derived from simultaneous blood sugar determinations by both methods on 90 separate samples of blood, ranging from 48 to 287 mg per 100 cc by the Folin-Wu method, and from 28 to 255 mg per 100 cc by the Somogyi procedure.

that the symptoms occurred toward the end of a meal or almost immediately after its completion (Table I) The meals that were alleged to produce the most severe symptoms were either those that contained more sugar and fluids than others or the heaviest meals of the day (Table II) Milk was thought to be a culprit by several, sweet substances by others A chocolate milk shake on an empty stomach was followed by unusually severe symptoms in two instances

The symptoms were observed to occur in 13 of the 16 patients who ingested a mixed meal They occurred toward the end of, or shortly after, consuming the test meal (Table II, Fig 1), which consisted of the following

TABLE II—*Food Substances Claimed by Patients to Produce "Dumping" Symptoms and Character of Response to Various Test Substances*

Case No	Substances or meals Which Patient Claimed Produced Severest Symptoms	"Dumping" Symptoms Reproduced (+) or not reproduced (0) by Oral Administration Of			
		Test Meal (See Text)	Glucose or Sucrose	Levulose	Protein hydrolysate
1*	Milk, desserts	+	+		
2*†	Milk desserts	+	+		
3†	Milk, cake milk shake	+			
4*	Large meals	+	+	+	+
				(diarrhea)	(vomited) (vomited)
5*†	Milk coffee, sugar	+	+		
6*†	Anything sweet	+			
7	Large meals	+			
8	Milk sweet substances	+		0	0
				(diarrhea)	(diarrhea)
9*†	Milk, cake, coffee, sugar	+	+	0	
				(diarrhea)	
10*†	Liquids with meals	+			0
					(diarrhea)
11	Milk, pastry	+		0	
				(diarrhea)	
12*	Milk, heavy meals milk shake	+	+		
13*	Milk	+			
14	Protein hydrolysate and dextri-maltose supplements	0	+		
15	Milk, sweet desserts	0	0	0	0
		(diarrhea)	(diarrhea)	(diarrhea)	(diarrhea)
16	Sweet desserts	0	0		0
		(diarrhea)	(diarrhea)		(diarrhea)

* 'Dumping' symptoms after meals prevented by atropine administered before meals

† 'Dumping' symptoms did not occur when fluids were omitted during meals

items Cooked cereal, 150 Gm , cream, 100 cc , milk, 240 cc , sugar, 15 Gm , toast, 30 Gm , butter, 10 Gm and 1 soft boiled egg This meal, on calculation, contained 75 Gm of carbohydrate, 25 Gm of protein, and 38 Gm of fat They appeared promptly, increased in severity and then gradually abated over a period of 10 to 40 minutes They were associated with tachycardia and an increase in the systolic and the diastolic blood pressure In three of the patients, "dumping" symptoms did not develop In one of them (Case 14), who had a small stoma associated with a "cup and spill" type of gastroenterostomy arrangement, the symptoms occurred only when a hypertonic solution of a protein hydrolysate and dextri-maltose was taken, although this followed a meal, which itself had given no "dumping" manifestations In the remaining two patients (Cases 15 and 16) loud borborygmi were heard, abdominal

THOMAS E MACHELLA

cramps were complained of and a bowel movement occurred shortly after completing the meal Both of these patients were sent to the clinic because they had had typical "dumping" symptoms previously (Table I)

2 Relationship of Time of Occurrence of Symptoms to Blood Sugar Concentration A (Following a mixed meal) Correlation of the symptoms which

FIG 1

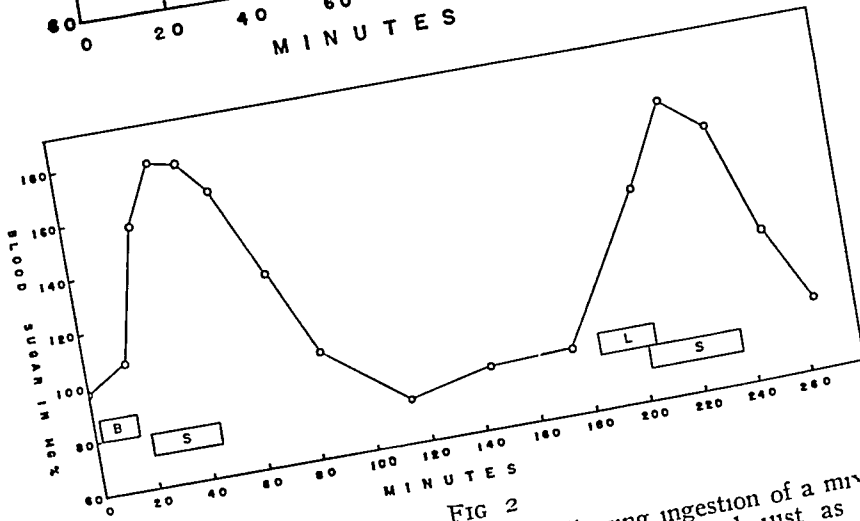
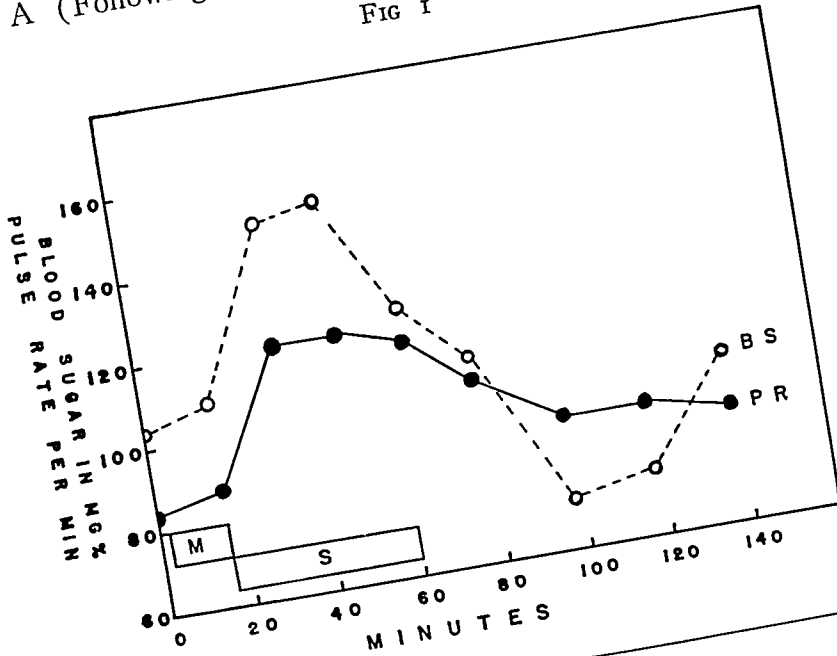


FIG 2

FIG 1—Case 6 Blood sugar curve following ingestion of a mixed meal (M) The "dumping" symptoms (S) appeared just as the meal was completed and were accompanied by an increase in pulse rate (P R) and blood pressure

FIG 2—Case 1 Blood sugar curves after breakfast (B) and lunch (L) The "dumping" symptoms (S) appeared shortly after breakfast was completed and again after lunch

occurred after a mixed meal, with the blood sugar concentration revealed that they occurred in all patients during the period of hyperglycemia (Figs 1 and 2) and began to abate as the blood sugar fell In none of the patients were late postprandial symptoms observed, i e, at a time when a reactive hypogly-

cemia might have been expected to occur, symptoms, however, did promptly follow the ingestion of a second meal (Fig 2)

B (Following oral administration of glucose or sucrose) Shortly after the ingestion of 100 Gm of glucose or sucrose in 250 cc of tap water unusually severe "dumping" symptoms appeared in 7 out of 10 instances (Table II), and persisted during the period of hyperglycemia (Fig 3) These symptoms were always more severe than those observed following mixed meals In only one, instance (Case 4), was a sensation of hunger and apprehension experienced in the post-hyperglycemic phase, at a time when the blood sugar level was low

In two patients (Cases 15 and 16) "dumping" symptoms did not occur following ingestion of sucrose or glucose (Table II) In one of them (Case 15), a liquid stool was passed shortly after the administration of the sucrose solution, and on another occasion after the ingestion of glucose The "dumping" symptoms did not occur despite a considerable elevation in blood sugar In the other (Case 16), the glucose solution was mixed with barium and the behavior of the barium observed fluoroscopically Marked intestinal hypermotility was noted and the barium was passed by rectum 15 minutes after its ingestion

3 *Comparison of Effects of Glucose Administered Orally and Intravenously* The injection of 0.5 Gm/Kg of glucose intravenously, in the form of a 50 per cent solution, was not followed by the development of symptoms or signs of the "dumping" syndrome (Cases 1 and 4, Table II), despite the fact that the blood sugar levels obtained were as great or even greater than those obtained following oral administration of glucose (Fig 3) An elevation in blood pressure or an increase in pulse rate likewise did not occur

4 *Effect of Ingestion or Instillation of Hypertonic Solutions Other than Glucose or Sucrose into the Small Intestine* A (Protein hydrolysate) The oral administration of 75 to 100 Gm of an enzymatic casein digest in 250 cc tap water to two patients (Cases 4 and 16) was promptly followed by the development of unusually severe "dumping" symptoms (Table II) In both instances the symptoms were terminated by vomiting the entire amount within five minutes of ingestion On another occasion, the solution was introduced, by means of a tube, directly into the jejunum (Case 4) in order to avoid a possible psychic effect of its unpalatable taste Emesis of the administered amount likewise promptly terminated the severe symptoms that followed In three other instances (Cases 8, 9 and 16) the ingestion of the solution did not produce "dumping" symptoms or vomiting but gave rise to a diarrhea B (Levulose) Four patients (Table II) ingested 100 Gm of levulose in 250 cc of tap water "Dumping" symptoms did not occur in three of them (Cases 8, 9 and 11), instead, loud borborygmi and numerous violent diarrheal discharges, consisting mostly of fluid, occurred shortly afterwards One patient (Case 4), however, experienced mild "dumping" symptoms prior to an ensuing diarrhea A similar diarrhea and absence of "dumping" symptoms was noted in Cases 15 and 16 following ingestion of sucrose or glucose

FIG 3 (Legend on opposite page)

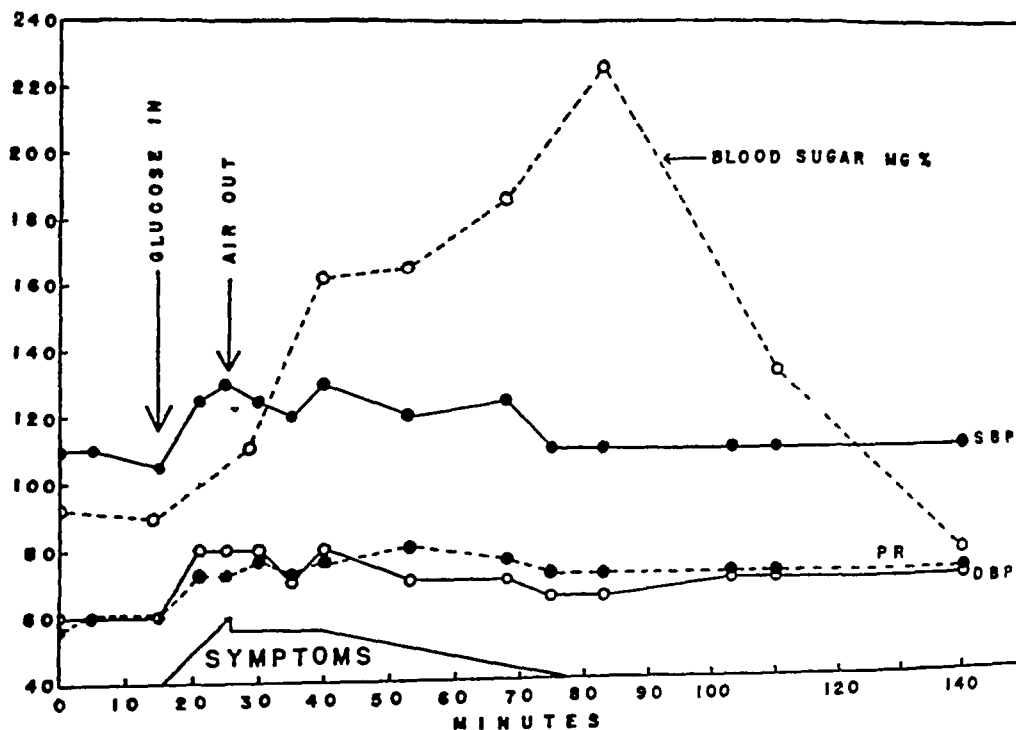
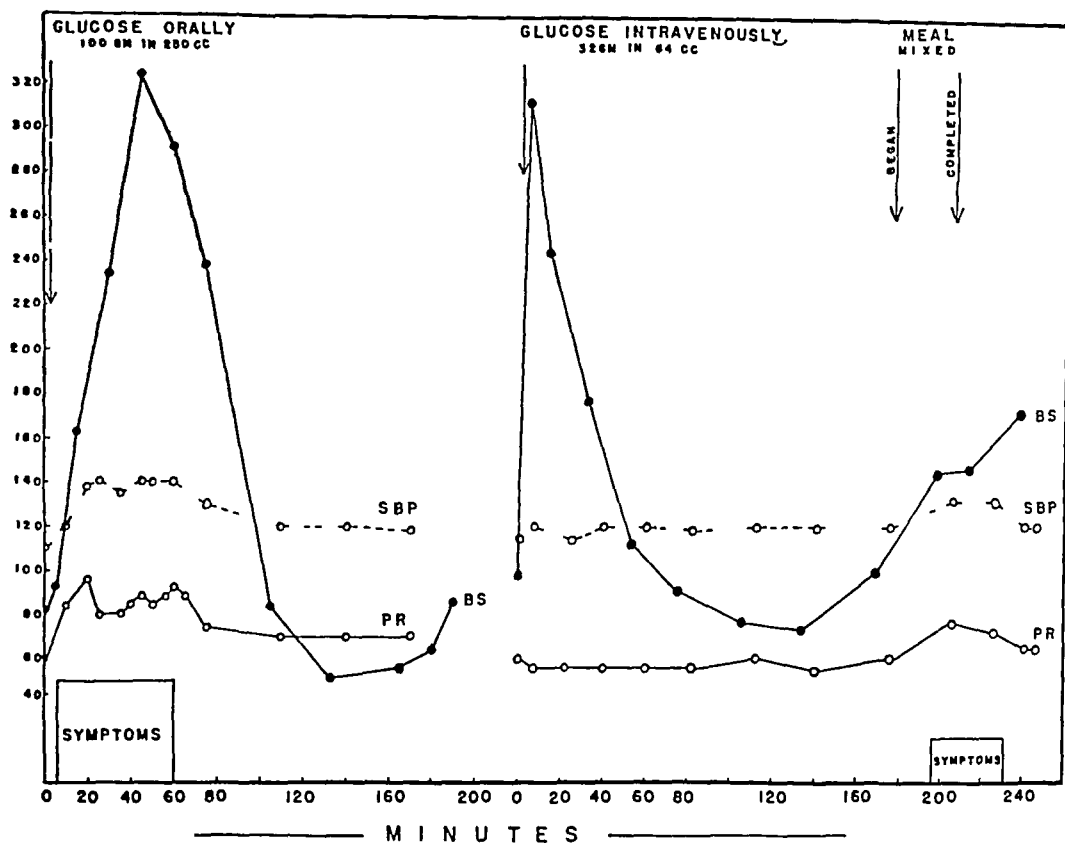


FIG 4 (Legend on opposite page)

5 *Effect of Instillation of Hypertonic Glucose Solution into an Isolated Segment of Intestine* The jejunum of a normal young healthy adult male (stomach intact) was intubated with a double-lumen Miller-Abbott tube, one lumen of which was connected to a balloon and the other arranged to deliver a solution of hypertonic glucose into a section of the jejunum proximal to the balloon. The balloon was inflated with sufficient air to obturate the lumen but not produce manifestations of gut distention. Then 250 cc of a solution containing 100 Gm of glucose were introduced into the isolated segment of jejunum. Within five minutes after the solution had entered, the patient broke out into a sweat, experienced nausea and became pale. The pulse rate and blood pressure increased (Fig 4) and he made an unsuccessful effort to withdraw the tube. The balloon was quickly deflated with a prompt lessening in severity of symptoms. They persisted, however, in milder degree for about 50 minutes. The symptoms were greatest in intensity before the blood sugar became elevated.

6 *Volume of Fluid Aspirated from an Isolated Loop of Intestine Following Introduction of a Hypertonic Salt Solution* By means of an intubation technic⁷ used for studying absorption from an isolated segment of intact intestine, 30 cc of a saturated solution of sodium sulfate were introduced into the upper jejunum of 20 subjects with intact gastro-intestinal tracts. Continuous aspiration, at a point 75 cm below the area into which the solution was introduced, yielded a flow of fluid at an average rate of 80 cc per minute during a 30-minute collection period. This was in contrast to an average rate of 0.8 cc per minute for collection periods varying from 7 to 150 minutes before the sodium sulfate was introduced. "Dumping" symptoms were observed in nine of the 20 subjects after the instillation of the sodium sulfate, in two of them the experiment had to be terminated because of their severity.

7 *Effect of Distending the Intestine by an Air-Inflated Balloon* Distention of the efferent jejunal loop by an air-inflated balloon (Cases 4 and 15) was followed immediately by pain in the epigastrium, palpitation, sweating, weakness and an increase in blood pressure (Fig 5). The severity of the symptoms was directly proportional to the degree of distention. The symp-

FIG 3—*Case 4* Blood sugar curves after administration of glucose orally and intravenously, and after a mixed meal. The "dumping" symptoms occurred when the glucose was administered orally but not when it was injected intravenously. They also occurred after the mixed meal. An increase in pulse rate (P R) and systolic (S B P) and diastolic blood pressures occurred during the period of symptoms produced by the mixed meal and the oral glucose solution, but not when the glucose was injected intravenously. In this and subsequent figures, the ordinates represent blood sugar in mg per 100 cc, pulse rate per minute, and blood pressure in mm mercury.

FIG 4—The figure illustrates the production of "dumping" symptoms in a normal subject by the instillation of 100 Gm of glucose in 250 cc water into a balloon-isolated section of jejunum. The symptoms were of such severity that the balloon had to be deflated. They appeared before the blood sugar concentration increased sufficiently to be termed a hyperglycemia and were accompanied by an increase in pulse rate (P R) and systolic (S B P) and diastolic (D B P) blood pressures. The manifestations of the "dumping" syndrome persisted in a less severe degree for about 50 minutes after the balloon was deflated.

toms and circulatory changes promptly abated when the balloon was deflated. Re-inflation reproduced the symptoms.

8 *Effectiveness of Atropine in Prevention of "Dumping" Symptoms* Atropine, in sufficient dosage to produce dryness of the mouth (0.6 to 1.2 mgm), administered one-half to one hour before meals, was effective in preventing "dumping" symptoms in nine out of 11 patients (Table II). The symptoms did occur, however, when a placebo was substituted (Fig 6). The effective use of atropine did not influence the blood sugar concentration (Fig

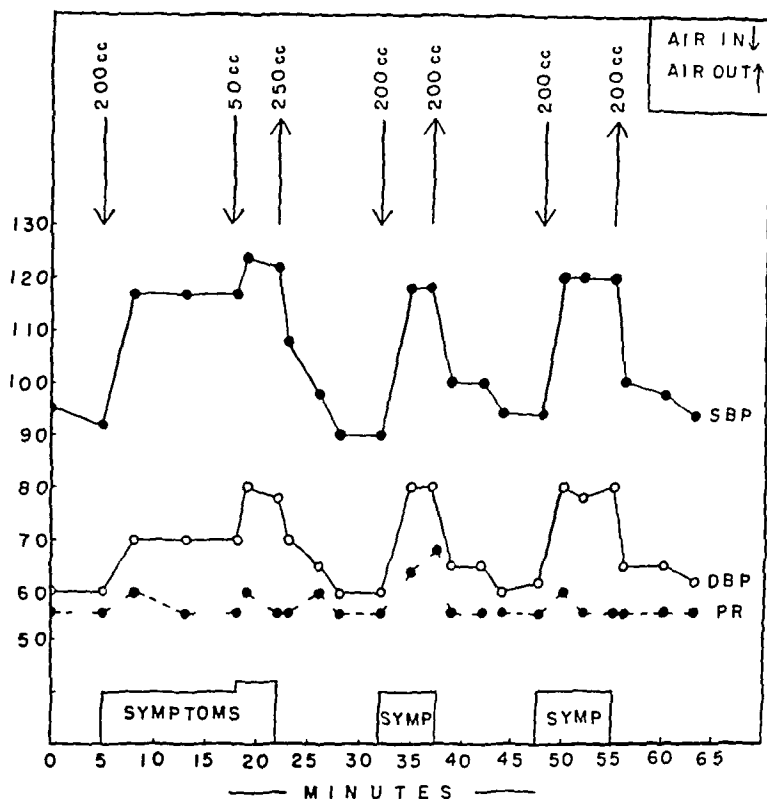


FIG 5—Case 15 The reproduction of the manifestations of the "dumping" syndrome by balloon distention of the efferent jejunal loop in a patient who had had "dumping" symptoms previously, but who developed diarrhea and not "dumping" symptoms when a hypertonic solution of glucose was administered orally or when a mixed meal was ingested (See Table II). Inflation of the balloon with air produced the symptoms and an increase in systolic (S B P) and diastolic (D B P) blood pressures. Deflation of the balloon caused the symptoms to disappear and the blood pressure to return to normal levels.

7) In two of the 11 patients (Cases 8 and 16) to whom atropine was administered prior to the ingestion of the meal, vomiting occurred as soon as the meal was eaten and a further trial of the drug was discontinued. The "dumping" symptoms were not prevented by vagotomy, "complete," as judged by negative insulin tests, in four of the patients (Cases 2, 3, 5 and 8).

9 *Effectiveness of Atropine in Prevention of Symptoms Due to Balloon Distention of Intestine* Air-inflation of a balloon in the efferent jejunal loop

POST-GASTRECTOMY "DUMPING" SYNDROME

before the administration of atropine produced the symptoms described previously. Re-inflation of the balloon after atropine was administered produced less severe symptoms than before atropine (Fig 8). The blood pressure elevation likewise was less marked. The pulse rate, however, increased as a result of the effect of atropine on the cardio-inhibitory mechanism, the rate remaining elevated even when the balloon was deflated.

FIG 6

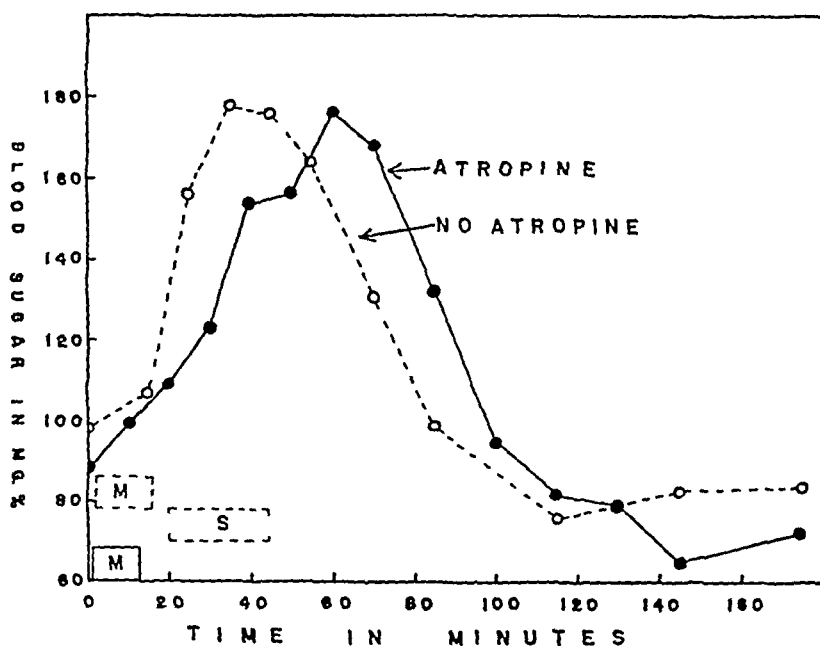
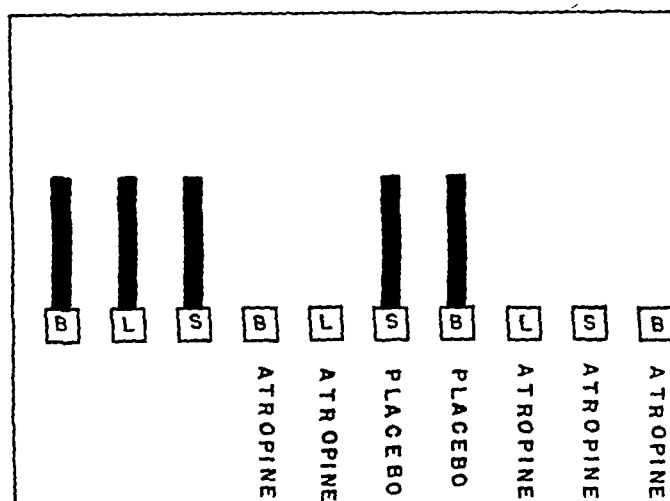


FIG 7

FIG 6—Case 1 The effect of atropine (gr 1/75) administered orally one-half hour before breakfast (B), lunch (L) and supper (S) on successive days. The "dumping" symptoms (dark columns) occurred when nothing, or a placebo, was administered but did not occur when atropine was given.

FIG 7—Case 1 Atropine sulfate (gr 1/75) administered subcutaneously prevented the "dumping" symptoms (S) from occurring after a mixed meal (M) but did not alter the blood sugar curve significantly.

FIG 8

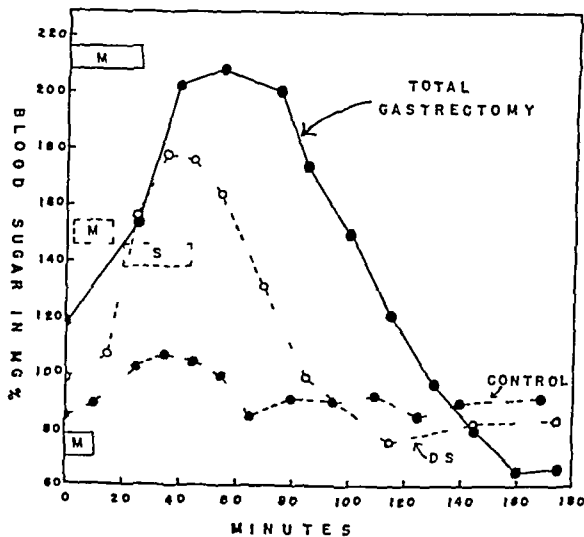
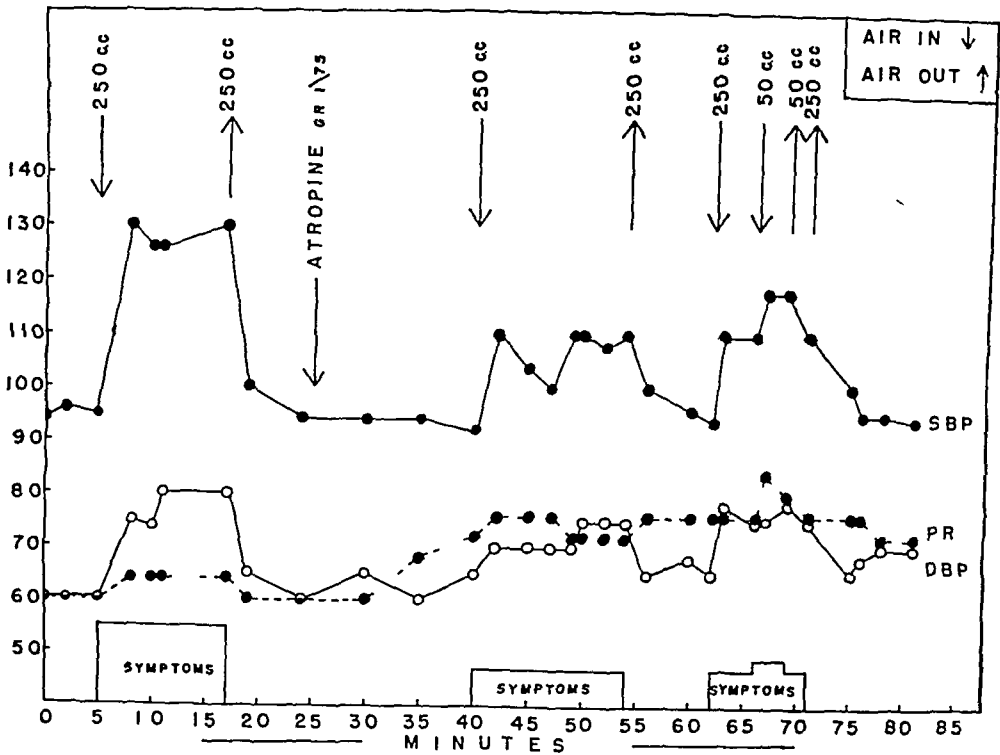


FIG 9

FIG 8—Case 15 Distention of the efferent jejunal loop by means of a balloon after atropine (gr 1/75) was administered subcutaneously, produced less marked "dumping" manifestations than before atropine. The symptoms after atropine were less severe as indicated by the height of the blocks and the increase in systolic (SBP) and diastolic (DBP) blood pressures was less marked. The pulse rate (PR) increased and remained elevated as a result of the atropine (See text).

FIG 9—Blood sugar curves in three subjects following ingestion of a meal (M) of exactly identical composition (See text). The curve labelled "control" was obtained in a healthy individual with stomach intact. The curve (DS) was obtained in a patient (Case 1) who had a subtotal gastrectomy performed and was manifesting "dumping" symptoms after meals. The solid black-lined curve was obtained in an individual who had his stomach completely removed, in him, no "dumping" symptoms occurred after the meal despite the fact that the blood sugar concentrations attained were greater than in the subject manifesting "dumping" symptoms (S).

10 *Effect of Omitting Fluids and Sugar from a Meal* The omission of sugar and of free fluids in form of soup, water, coffee, milk, etc., during meals, in each of our last six patients observed (Cases 2, 3, 5, 6, 9 and 10), resulted in a failure of the "dumping" symptoms to occur. Fluids, taken between meals, caused no symptoms unless they contained sugar.

COMMENT

On the basis of the experiments described in this report supported by the data of other workers, the following explanation of the mechanism of production of the early postprandial "dumping" symptoms seems tenable. They are caused by distention of the jejunum. This distention ordinarily is due to an outpouring of fluid by the jejunal wall in an attempt to dilute hypertonic food material that has been passed along by the non-retentive stomach rather than to the mechanical presence of the ingested food per se. The symptoms are not caused by hypoglycemia or hyperglycemia, though hyperglycemia may be present during the period of symptoms if the particular hypertonic solution responsible for their production happens to be a sugar solution such as sucrose or glucose.

In support of the proposed mechanism are the following clinical and experimental observations: 1. *The symptoms occur toward the end of or shortly after the completion of a meal*, at which time a hypertonic solution may first be made available to the jejunum for dilution. It is possible, however, for symptoms to occur some time after the completion of a meal if the stoma is small and not situated in the most dependent portion of the gastric remnant. In such an instance, the gastric remnant does not empty promptly and is of the "cup and spill" type. The mechanism is brought into play only as the gastric remnant spills hypertonic contents into the jejunum. This occurred in one of our patients (Case 3) who manifested symptoms only when he took supplemental feedings of a casein hydrolysate and dextrin-maltose solution after eating his main meal.

2. *The absence of any consistent correlation between symptoms and blood sugar concentration is noted.* Despite the fact that a hyperglycemia may be demonstrated during the period of symptoms induced by the ingestion of a mixed meal or of a sucrose or glucose solution, one should not ascribe the production of symptoms to the hyperglycemia for several reasons.

(a) "Dumping" symptoms can be demonstrated to occur before hyperglycemia develops following the intrajejunal instillation of glucose solution (Fig. 4).

(b) "Dumping" symptoms do not occur when hyperglycemia is induced by the intravenous injection of glucose. The absence of "dumping" symptoms after intravenous injection of glucose has been commented on by Gilbert and Dunlop.¹

(c) The blood sugar concentration may rise to a considerable height after a meal in a completely gastrectomized patient (Fig. 9) and yet no "dumping" symptoms occur.

(d) "Dumping" symptoms may be produced by the administration of hypertonic solutions of magnesium and sodium sulfate, which do not produce a hyperglycemia. We have observed "dumping" symptoms after the instillation of magnesium sulfate into the duodenum of patients being subjected to biliary drainage for evidence of gallbladder disease.

3 *The "dumping" symptoms can be reproduced by balloon distention of the intestine.* This strongly supports the mechanical distention hypothesis. Similar symptoms were noted by Ivy⁸ following irritation of the duodenum. He also reported the production of pain in the epigastrium on distending a balloon in the duodenum. We have frequently noted "dumping" symptoms during distention of a balloon-isolated segment of duodenum with injected barium when attempting to delineate duodenal mass lesions by roentgenological means. At times the procedure had to be discontinued because of the severity of the symptoms. However, it is not the distention produced by the mechanical bulk of an ingested meal alone that gives rise to the "dumping" symptoms because, as has been also noted by others,⁵ not all meals are followed by "dumping" symptoms. To produce symptoms, a meal should possess several characteristics and certain conditions must be present.

(a) Ingredients of high osmotic pressure (over 300 milliosmols) must be present in the meal. The ingredients are usually sugars but can be salt and protein products.

(b) Sufficient fluid must be ingested during a meal to dissolve the ingredients possessing osmotic properties and yet yield a hypertonic solution of sufficient strength to draw additional fluid from the blood stream into the gut. The omission of fluids from the meals of several of our patients resulted in the failure of "dumping" symptoms to develop.

(c) The energy expended by the diluting mechanism in distending the lumen must not be dissipated by vomiting. Vomiting of the meal can provide complete relief from the symptoms by removing the cause of the distention. "Dumping" symptoms are claimed to be lessened when the patient lies down after a meal. In the horizontal position jejunal content flows back into the gastric remnant. Thus, the energy, which otherwise would be fully utilized in distending the gut, is partially dissipated.

(d) The energy expended by the diluting mechanism must not be dissipated by the production of such excessive hyperactive peristalsis that the meal is dispersed rapidly throughout the small intestine. "Dumping" symptoms may fail to occur if a stool is passed shortly after ingestion of sugar solution or a meal, when such stool passage is the result of hyperactive small intestinal peristalsis stimulated by a hypertonic solution in the jejunum. Evidence in support of such a mechanism was supplied by Abbott, Karr and Miller⁹ employing roentgenologic, balloon-kymographic and chemical analytic methods. They found that the propulsive activity of the small intestine increased directly as the concentration of glucose introduced.

The tendency to incite diarrhea rather than "dumping" symptoms appears

to be more characteristic of equivalent concentrations of levulose than of sucrose of glucose, as evidenced by the observations on four of the patients (Cases 4, 8, 9 and 11), when violent diarrheal discharges occurred after ingesting levulose. Two of the patients (Cases 15 and 16) did, however, develop diarrhea and not "dumping" symptoms after glucose or sucrose. It is of interest to note that in the protocols of Glaessner's² cases, diarrhea and not "dumping" symptoms occurred when levulose was administered. He ascribed the failure of "dumping" symptoms to occur after levulose to its poor absorption and absence of the hyperglycemia which he believed to be responsible for "dumping" symptoms.

(e) Fluid must be readily mobilized from the blood stream to enter the gut lumen with sufficient rapidity to distend it. That such fluid does enter the intestine in response to the presence of a hypertonic solution is evidenced by the ability to aspirate several times the volume of a hypertonic sodium sulfate solution introduced into an isolated segment of intestine within a short time of its entry. Similar observations were reported by Abbott, Karr and Miller⁹ when hypertonic glucose solutions were introduced. Pendergrass *et al*¹⁰ reported roentgenologic evidence of dilution of a hypertonic solution in the intestine when they administered a hypertonic glucose solution containing barium to subjects who emptied the meal promptly. The intestinal stream of barium was observed to produce a cloud effect "as though the hypertonic solution caused mucosa to pour fluid in an attempt to dilute the opaque medium." A dilution of hypertonic solutions introduced into the stomachs of dogs was reported by Ravdin *et al*,¹¹ who suggested that this mechanism prevented hypertonic solutions from entering the intestine.

That many of the manifestations of the "dumping" syndrome can be reproduced by inflating a balloon in the intestine is strong evidence in support of the distention theory of production of symptoms. There is, however, one point which requires comment. In our experience, balloon distention of the gut, sufficient to produce symptoms similar to the "dumping" manifestations, always gave rise to severe pain in the epigastrium. Only three of our 16 patients complained of pain as one of the "dumping" manifestations following meals. Others, however, complained of a "fulness" or a "tightness" in the epigastrium, similar to that experienced before actual pain occurred on inflating the balloon. Whether or not pain occurs, or just tightness, may be a matter of degree, as well as of the extent of the area of distention. It is of interest that Magee and Reid¹² have shown that hypertonic glucose solutions, introduced into the gut, stop the movement of villi and slow the blood flow through the mucosal vessels. The accelerator response of the cardiovascular system which occurs during the "dumping" symptoms may represent a compensatory attempt to increase the blood flow through the congested mucosal vessels.

4 *The symptoms can be prevented by omission of fluids from the meals.* The failure of "dumping" symptoms to occur when liquids are omitted from the meal has led us to adopt such a regimen for the prevention of "dumping"

symptoms Liquids are ingested between meals Atropine, because of its tendency to produce a disturbing dryness of the mouth and blurring of vision, is not used routinely Some of the patients, however, take atropine when they wish to eat a full course meal

MECHANISM OF ACTION OF ATROPINE IN PREVENTING "DUMPING" SYMPTOMS

In our experience, the administration of atropine in physiologic doses before a meal was effective in preventing the early postprandial symptoms in most instances Bockus¹³ presumably referring to symptoms due to rapid emptying of the stomach after partial gastrectomy, also noted that large doses of atropine or belladonna may be of benefit It should be emphasized that it is the early postprandial symptoms which may be prevented by atropine The late manifestations, which are due to hypoglycemia, are apparently not influenced¹ At the present time, the exact mechanism by which atropine prevents the early postprandial "dumping" symptoms is not clear and the problem is being studied further The drug as demonstrated by Elsom and Drossner¹⁴ lessens intestinal tone, diminishes muscular contractions and, as a result, decreases intestinal motility In the "dumping" patients it may possibly act by relaxing the gut beyond the point at which active distention is produced by the pouring in of fluid This explanation is suggested by the experiment cited in Fig 8 The mechanism does not appear to be the interruption of an afferent or an efferent pathway in the vagus nerves because vagotomy, "complete," as judged by negative insulin tests, does not prevent the symptoms One of Moore's cases¹⁵ also manifested "dumping" symptoms after vagotomy In our experience a physiologic dose of atropine has more consistently produced an inhibitory effect on the small intestine than has vagotomy We have in our series of cases, one patient (Case 8) who developed jejunal dilatation after vagotomy¹⁶ and who manifests "dumping" symptoms

SUMMARY

1 Observations on 16 subtotal gastrectomy patients manifesting symptoms of the "dumping" syndrome revealed that the symptoms occurred toward the end of a mixed meal or immediately thereafter, during which time the blood sugar concentration was always elevated They were accompanied by a rise in blood pressure and an increase in pulse rate Hypoglycemia was not found in any of them during the period of symptoms

2 The "dumping" symptoms were reproduced by the administration of glucose and sucrose orally but not when glucose was administered intravenously

3 The "dumping" symptoms were reproduced in individuals with intact stomachs as well as in patients subjected to subtotal gastrectomy, by the intrajejunal instillation of hypertonic solutions of glucose protein hydrolysate and sodium sulfate, and by distention of the jejunum with an air-inflated balloon They have also been observed following the introduction of 33 per cent

magnesium sulfate into the duodenum for the purpose of evacuating the gallbladder

4 The symptoms were prevented by the omission of fluids from meals as well as by the administration of atropine in physiologic doses before meals. They were not prevented, however, by vagotomy.

5 It is proposed that the early postprandial "dumping" symptoms are due to distention of the jejunum by fluid which enters the lumen of the gut from the blood stream in response to the presence of a hypertonic solution formed from the ingredients of a meal possessing osmotic properties and not to distention by the bulk of the ingested food. They are not caused by hyperglycemia though a hyperglycemia may be present during the period of symptoms.

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A STUDY OF MORTALITY IN A BURNS UNIT*

STANDARDS FOR THE EVALUATION OF ALTERNATIVE METHODS OF TREATMENT

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DURING THE LAST 30 years, medical science has introduced a wide range of potent remedies. For many diseases (and injuries) the new treatments available do not consist of the simple administration of a single drug, rather, multiple advances have been introduced. This more complex situation is well exemplified by the modern treatment of burns. To assess the value of such all-round improvement, the results of treating a comprehensive series of patients must be described in quantitative terms. As ordinarily presented, however, without statistical analysis, these results are frequently meaningless, and surprisingly little critical interpretation has been offered. Bare statements such as "seven thousand patients were treated with a case mortality of five per cent" are still common in medical literature. The following account is intended to show how such work can be converted into valuable data. The methods used involve a statistical treatment which is not familiar to most medical men. A simple table (Table III) has been drawn up which, by arithmetical addition only, permits a comparison between the results of treatment to burned patients given in the Medical Research Council Burns Unit and that used in other centers. In effect, a simple standardization of the results is achieved by these calculations so that account is taken of the differences in severity of lesion and age of patients in each series. The technical methods by which this table has been produced are given in full, so that their validity can be checked, and in order to bring out various interesting implications of the results. It is hoped that the essentials of the method will be applied to conditions other than burns.

The two factors which need standardizing, if results of different centres are to be validly compared, are age of patient and severity of lesion.

(a) *The age* of each patient is easily obtained, and as is well known, has a very marked effect on the outcome of a burn especially in later adult life. It is therefore desirable to record individual ages rather than to assign the patients to coarse age-groups.

(b) *The severity* can be measured by the proportion of the body surface burned (Berkow^{1, 2}). It has become customary to grade patients on this basis, and clinical impressions have been formed as to the extent of burning likely to cause death, thus a full thickness burn of one third of the body surface was at one time regarded as inevitably fatal. Exact studies have confirmed that burn area is a useful criterion of severity (Colebrook, *et al*,⁹ Clarkson and Lawrie,⁵ Morrison¹²). Clearly, therefore, the overall mortality of a series

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MORTALITY IN A BURNS UNIT

measure of severity Most of the patients in this series had areas of both full- and partial-thickness skin loss, and the area of each was recorded By plotting the results from these patients on a diagram showing deep and superficial

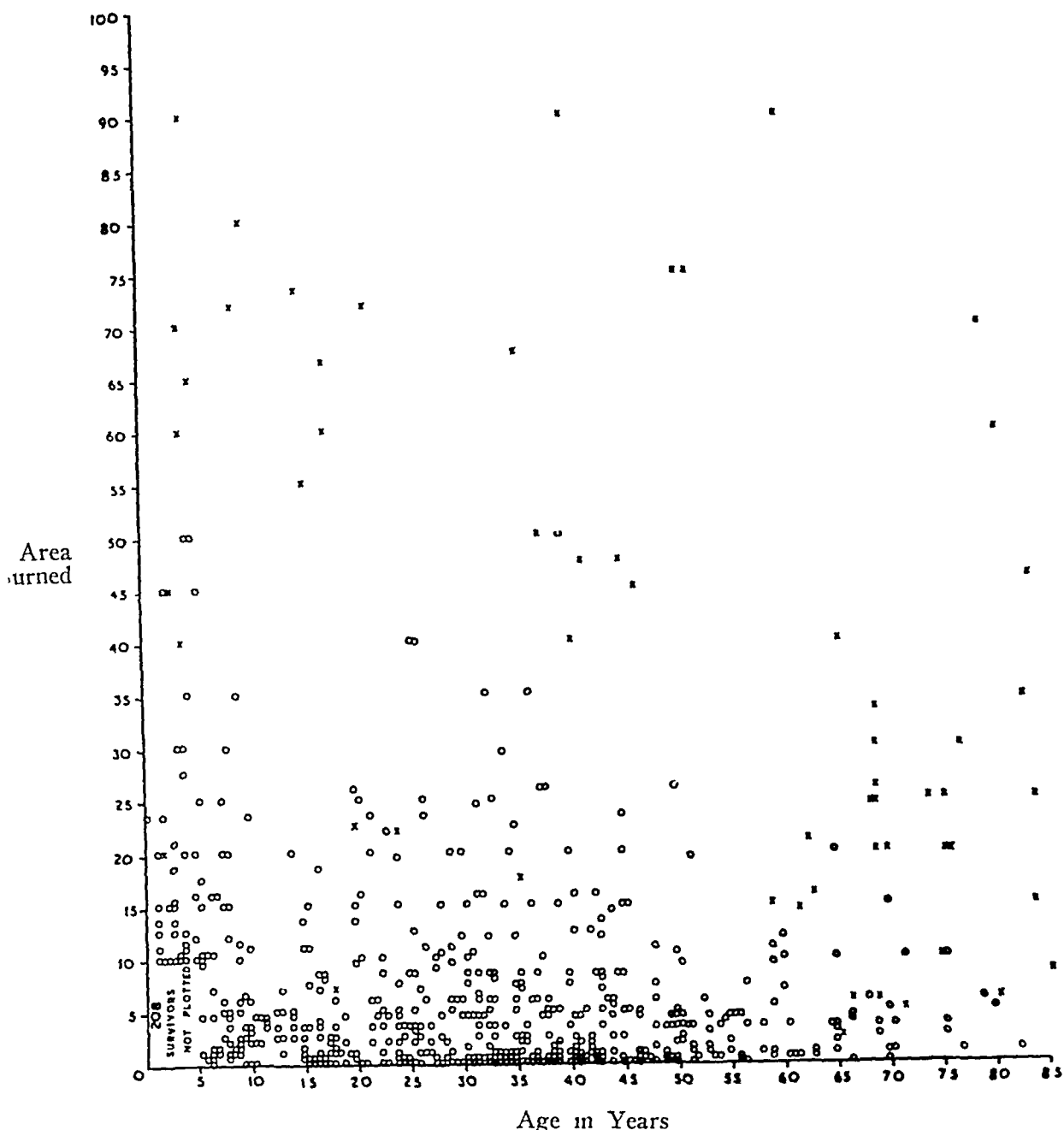


FIG 2—Diagram showing the distribution of the 794 patients in respect of (a) age in years, (b) burn area expressed as percentage of total body surface
Patients who survived shown — o, died — x

areas, the trend of mortality was found to be best expressed in terms of “deep area plus one-fourth superficial area,” *i e*, area for area a deep burn seemed to be four times as serious as a superficial burn This refinement might be of value in comparing closely matched and highly documented cases, but since the exact diagnosis of burn depth is often difficult, subject to revision during the

healing stages, and likely to vary with the judgment of different clinicians, the more simple if less accurate measure based on the total area of the burn has been adopted

Since the two factors, age and area burned, influence the mortality, it is convenient at first to consider only one factor, the severity of the burn, by dividing the series into suitable age groupings. For this purpose, patients with ages 0 to 14, 15 to 44, 45 to 64, and 65 or more years were studied separately. By calculating the proportion of patients dying with burns of differ-

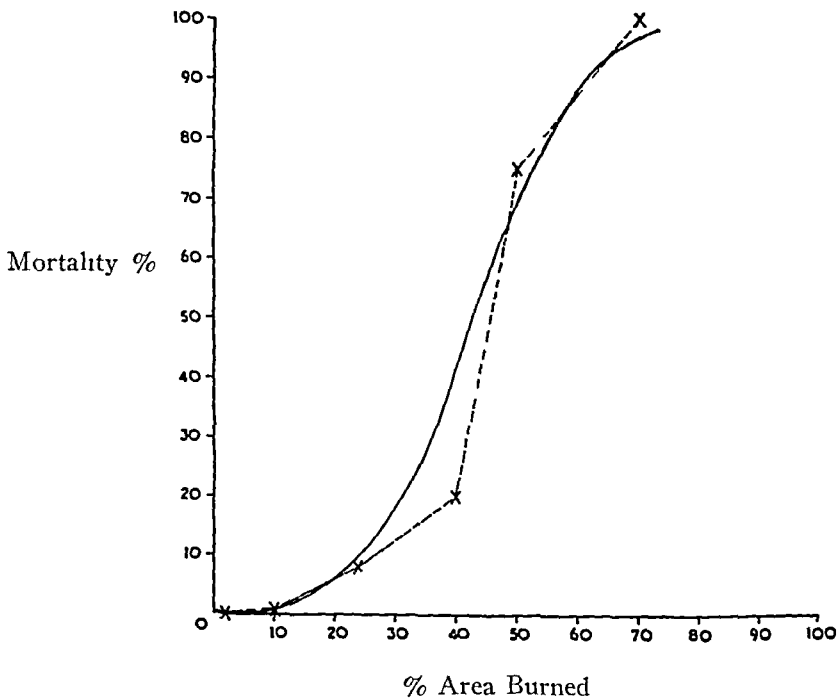


FIG 3—Diagram illustrating characteristic relationship between case mortality (percentage of patients dying) and severity index based on percentage area burned, plotted for various area groups of patients 15 to 44 years old. Solid line represents Probit fit

ent areas within each group, rough curves relating case mortality to the percentage area burned could be constructed. Such a graph is shown in Figure 3. The data plotted in this way suggest an S-shaped curve similar to that found by Clarkson & Lawrie.⁵ Such a sigmoid relationship implied that even for relatively mild burns (*e g*, 5 to 15 per cent in adults age 15 to 44) a few individuals, less able than the average to withstand burning, succumb. On the other hand, although an insufficient number of severe burns are available to demonstrate the point with certainty, it is reasonable to assume that in the region of the curve where the mortality is tending to approach 100 per cent, there would be a few exceptionally strong individuals who would survive a burn severe enough to cause death in the "average" person. (This assumption is to an extent shown to be valid by the subsequent calculations.)

Those familiar with toxicity experiments on batches of animals, with the action of antiseptics on bacteria, or with many other biological studies involving populations of appreciable size, will recognize the essential similarity of this S-shaped curve to those plotted from other biological phenomena. For instance the mortality among batches of animals plotted against various doses of a toxic drug (or against the logarithm of these doses) usually shows a sigmoid relationship. It has been supposed that this form of relationship depends on the variation of one individual from another within any living population group—a variation in susceptibility about an average level which in quantitative degree corresponds with the usual “normal” distribution curve. In experiments with large numbers, this supposition has been tested and found to fit the facts, it can therefore be justifiably extended to cover an analogous situation such as the mortality from burns.

Early quantitative studies of this variation of susceptibility to toxic agents in animals were made by Gaddum¹¹. Since then, the mathematical technic for handling such material has been developed by Bliss,³ and in the form now known as “Probit Analysis” has been clearly explained and set out by Finney.¹⁰ So far as is known, this valuable method has not previously been applied to any mortality findings in man.

In essence, the Probit technic implies that data of the type shown in Fig 3 can be replotted with the vertical scale of response (percentage mortality in this case) altered so as to convert a sigmoid curve into a straight line. This result is obtained if the original sigmoid relationship depends on a “normally distributed” factor such as individual susceptibility. On the altered scale a Probit value of 5 corresponds to 50 per cent mortality, of 6 and 4 to 84 per cent and 16 per cent respectively, of 7 and 3 to 97.7 per cent and 2.3 per cent, etc. Having effected this straight line transformation, simple (though laborious) methods are available for calculating the best-fit formula for the data, testing the probable linearity of the relationship, assessing the certainty with which future results can be predicted and so on. In series suitable for considering in Probit terms, the conclusions are drawn from every part of the data, due relative importance being attached to each. Thus in the analysis of the burned patients, every death and every survival counts, while chance variations in the results from different groups are fitted in with the overall experience.

APPLICATION OF PROBIT ANALYSIS, AGE GROUPING RETAINED

The results plotted in Fig 2 were first grouped as shown in Table I. Within each age group is tabulated the number of patients who suffered burns affecting various proportions of the total body surface. Alongside is shown the proportion of patients which died in each sub-group.

Thus of five patients age 0 to 14 years with an approximate mean area burned of 50 per cent, one died, giving an observed case mortality of 20 per cent.

Table I affords the starting point for calculation of Probit values, and the results finally obtained are shown at its foot. The Probit lines drawn from

these formulae are shown in Figure 4. Here, the Probit values which constitute the vertical (or Y) scale are shown on the left, and the corresponding percentage mortalities are shown on the right. Mathematical testing shows that the lines afford a satisfactory fit with the original data, and gives no indication of a departure from linearity in the direct relationship between Probit values calculated from mortality and the percentage body area burned.

TABLE I—*Burns Mortality Results, Summarized from Figure 2, Used in Calculating Probit Values*

Age Group 0-14 Years			Age Group 15-44 Years		
Approx Mean Percentage Area Burned	Number of Patients	Observed Case Mortality	Approx Mean Percentage Area Burned	Number of Patients	Observed Case Mortality
2	191	0%	2	175	0%
10	107	0%	10	83	1 2%
20	23	4 3%	20	31	9 7%
30	6	0%	30	7	0%
40	3	33%	40	5	20%
50	5	20%	50	4	75%
60	1	100%	60	2	100%
70	4	100%	70	3	100%
80	1	100%	90	1	100%
90	1	100%			
Total number of patients in group 342			311		

Age Group 45-64 Years			Age Group 65† Years		
Approx Mean Percentage Area Burned	Number of Patients	Observed Case Mortality	Approx Mean Percentage Area Burned	Number of Patients	Observed Case Mortality
2	66	0%	2	14	7 1%
			6	9	55 6%
10	18	5 6%	10	3	33 3%
			15	2	50%
20	6	50%	21	6	100%
30	1	0%	30	8	100%
			35	1	100%
45	1	100%	45	1	100%
			60	1	100%
75	2	100%	70	1	100%
90	1	100%			
Total number of patients in group 95			46		

Probit formula obtained from above data

0-14 years $Y = 1.29 + 0.0728X$

15-44 years $Y = 1.94 + 0.0709X$

45-64 years $Y = 1.97 + 0.1343X$

65+ years $Y = 3.61 + 0.1532X$

(X = % area burned)

From the lines in Fig. 4 (or the formulae in Table I), estimates can readily be made of the severity of burn likely to produce any level of mortality. For instance, the severity corresponding to 50 per cent mortality can be read directly from Fig. 4, *e.g.*, in the 0 to 14 age group, a 51 per cent body area burn, on the basis of this series, is likely to produce death in 50 per cent of the patients treated. Just as the toxicity of a drug is best expressed in terms of the dose needed to kill 50 per cent of a batch of experimental animals

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(usually known as the Lethal Dose for 50 per cent or $L D_{50}$), so we may assess the treatment of a series of burned patients in terms of the area of burn producing death in 50 per cent of cases (*i e*, Lethal Area for 50 per cent, or $L A_{50}$) An improvement in treatment will be reflected in a rise in the $L A_{50}$ in a comparable group of patients The degree of certainty with which this figure can be given depends on the number of patients studied, and on how severely each one was burned, it can be expressed as falling between certain "fiducial limits," *i e*, the range within which the true result should be found 19

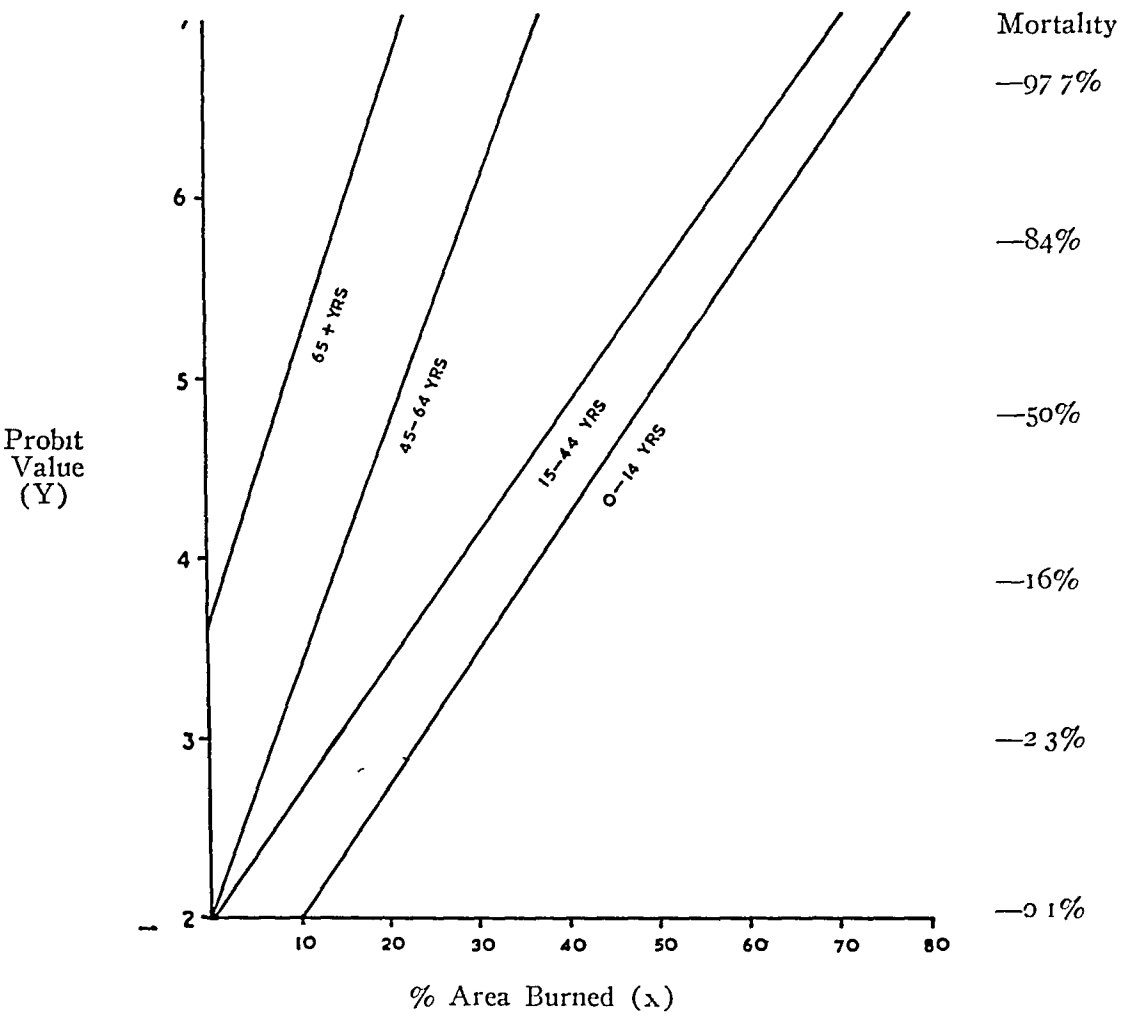


FIG 4—Probit values of case mortality related to severity index (*i e*, percentage area burned) for each age group, plotted from formulae given in Table I Typical results derived from this figure are shown in Table II

times out of 20 In Table II, the areas of burn found likely in this series of patients to produce 50 per cent and 25 per cent levels of mortality (the $L A_{50}$ and $L A_{25}$ values) are tabulated, together with the fiducial limits of these values

Table II shows clearly the quantitative effect of age in decreasing the patient's powers of resistance to burn trauma Thus among patients age 0 to 14 (average five years) it took a 51 per cent area burn to cause death in

50 per cent of cases, a corresponding effect was produced by a 23 per cent area burn in the age group 45 to 64 (average 55 years) and only a 9 per cent burn in the elderly group age 65 or more (average 71). These changes are highly significant.

RESULTS CO-ORDINATED TO SHOW MORTALITY EXPECTED AT ANY AGE

Ageing is a continuous process, and age grouping is an artificial, though convenient, abstraction. The results calculated for the series may now be considered as a whole by plotting graphically, the $L A_{50}$, $L A_{30}$, etc. against age. Such a diagram has been constructed in Figure 5. Each contour line showing the percentage area burn likely to produce death in 50 per cent, 30 per cent, etc., of cases is based on four points determined from the appropriate Probit line. The points show no suggestion of any discontinuity, and smooth lines have therefore been drawn between them. It is noticeable that there is no evidence, either in this graph or in the raw data, for a worse prognosis in very young children than in older children or adults with any given

TABLE II—*Comparative Lethality of Burns at Different Ages Derived from Probit results*

Age Group Years	Mean Age Years	No of Patients In Group	Area of Burn Corresponding to 50% Mortality		Area of Burn Corresponding to 25% Mortality	
			LA_{50}	Fiducial Limits*	LA_{25}	Fiducial Limits*
0-14	5	342	51%	43%-64%	42%	32%-54%
15-44	31	311	43%	37%-55%	34%	28%-42%
45-64	55	95	23%	17%-40%	18%	13%-28%
65 or more	71	46	9%	6%-15%	5%	0%-8%

* Fiducial limits have been calculated for $P = 95$ (i.e. range within which result may be expected to fall 19 times out of 20).

percentage area burn of the body. Since this is contrary to the clinical impressions of many surgeons, the original case notes have been carefully checked to exclude complicating factors (e.g., a preponderance of scalds rather than burns among young children). The conclusion appears sound, though it should be noted that the present series does not include any severely burned infants under one year of age (Fig. 1) so that no statement can be made about patients in this age group.

PRACTICAL METHOD OF COMPARING DIFFERENT SERIES

Any other long series can be compared with the results given here by repeating the calculations described above. After deriving Probit values, a statistical comparison could be made between the lines obtained, both in respect of their position (e.g., the $L A_{50}$ s) and of slope (i.e., the variability of susceptibility to burn trauma). Since the numbers of patients studied are usually less extensive and since the necessary calculations are tedious, a more convenient method of comparison is put forward.

From the mortality contours at all ages (Fig. 5), a grid (Table III) has been constructed showing the probability of death for any given combination

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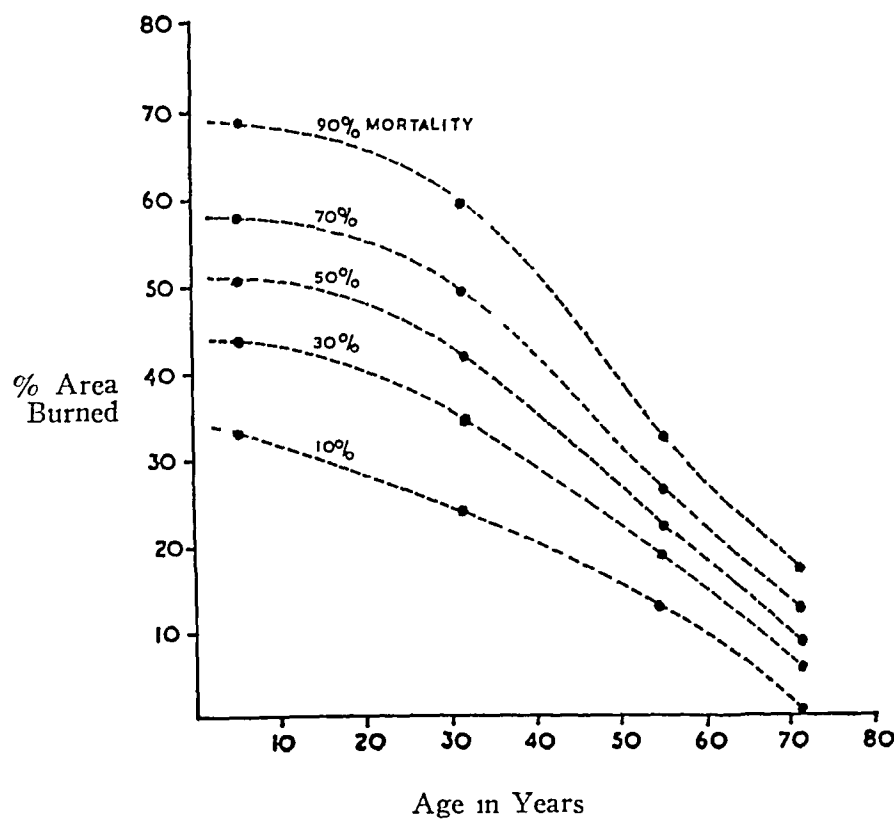


FIG 5 —Contour lines dividing zones of equal mortality with various combinations of age and severity The points are derived from the Probit values plotted in Figure 4, and have been used to prepare grid shown in Table III

TABLE III —Grid of Approximate Mortality Probabilities for Various Combinations of Age and Area

% of Body Area Burned	Age — Years															
	0- 4	5- 9	10- 14	15- 19	20- 24	25- 29	30- 34	35- 39	40- 44	45- 49	50- 54	55- 59	60- 64	65- 69	70- 74	75†
73 or more	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
68-72	9	9	9	9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
63-67	8	9	9	9	9	9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
58-62	7	7	8	8	9	9	9	9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
53-57	6	6	7	7	7	8	8	9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
48-52	5	5	5	5	6	7	7	8	9	1 0	1 0	1 0	1 0	1 0	1 0	1 0
43-47	3	3	4	4	5	5	6	7	8	9	1 0	1 0	1 0	1 0	1 0	1 0
38-42	2	2	3	3	3	4	5	6	7	8	1 0	1 0	1 0	1 0	1 0	1 0
33-37	1	2	2	2	2	3	3	4	5	7	9	1 0	1 0	1 0	1 0	1 0
28-32	1	1	1	1	1	2	2	3	4	5	7	9	1 0	1 0	1 0	1 0
23-27	0	0	0	1	1	1	1	1	2	3	5	7	9	1 0	1 0	1 0
18-22	0	0	0	0	0	0	1	1	1	2	3	5	7	9	1 0	1 0
13-17	0	0	0	0	0	0	0	0	0	1	1	2	4	7	8	1 0
8-12	0	0	0	0	0	0	0	0	0	0	0	1	2	4	6	8
3-7	0	0	0	0	0	0	0	0	0	0	0	0	1	2	3	6
0-2	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3

These figures are approximations to a single place of decimals. A reading of 1 0 therefore implies "most probable value greater than 0.95"

of age and burn area. These probabilities are shown as decimal fractions of unity so that a 90 per cent mortality appears as 0.9. All figures are given to the nearest decimal place. From the table set out in this way simple addition



FIG 6—Photograph on admission of a typical 25 per cent burn of a child $2\frac{1}{2}$ years old

will give the expected number of deaths. To use this table for comparative purposes, a list of patients treated should be prepared giving age and per-

centage body area burned. Each patient can then be given a probability of mortality from the table. For example a patient aged 5 years with a 40 per cent burn will be scored "0.2," another aged 50 with a 25 per cent burn will be scored "0.5" and so on through the list. The total number of deaths expected from the whole series is then obtained by addition of all the probabilities. This total must then be compared with the number of deaths actually experienced in the series. If this actual number is less than the expected deaths it suggests that better results have been obtained possibly as a consequence of improved treatment. It is not feasible to apply a conventional criterion of "significance" to such a comparison but any marked improvement or inferiority in treatment of a reasonable number of patients will be demonstrated.

This method will also show the particular type of patient contributing to any disparity. For this purpose, sub-totals, observed and expected, are compared, for example, for young and old patients, or for medium and large burns. In this way, it might be possible to demonstrate that another Burns Unit while sustaining about the expected number of deaths when all patients were considered, had substantially better results with old persons, but less good results with children. Such comparisons should clearly lead to an interchange of information with mutual advantages.

DISCUSSION

If the idea of a sigmoid relationship between mortality and burn severity is accepted then no matter how severely burned the patient may be, some probability of his survival remains. This statement is of great clinical importance, and is preferable to the old idea that a burn of a certain proportion of the body surface was necessarily fatal. If each burned patient is regarded as having a chance of recovery, every effort will be made to help by means of treatment. As pointed out in the footnote to Table III, the probabilities shown as 1.0 are only approximations indicating a mortality of over 0.95, *i.e.*, a chance of survival of less than 1 in 20. Such chances cannot be regarded in this clinical situation as negligible, and may increase with improved methods of treatment.

In this study, death or survival has been the only criterion of successful treatment considered. This limitation was intentional so as to simplify analysis and discussion. Quantitative indices of disability time or degree of final recovery would be susceptible to similar studies. Mortality also can be subdivided in the assessment of results into "early" and "late" deaths in relation to the time of being burned. In this series, there is little to indicate any marked alteration in the relative numbers of early and late deaths, as compared with pre-war studies. It is probably justifiable to conclude that roughly as many lives have been saved by improved resuscitation, especially with plasma transfusion, as by the control of infection.

Enough has been said to indicate the practical applications of this analysis to the evaluation of burn treatment. The technic should also be applicable to other conditions, though in each case suitable severity criteria must be worked

out These may take a simple physical form (*e g*, degree of trauma) clinical (raised or lowered blood pressure, basal metabolic rate), biochemical (liver function) or other forms based on instrumental findings such as the radiograph or electrocardiogram Again mortality need not be used to assess results, since many other findings can be transformed on to Probit scales

Apart from the importance of quantitative assessment in specific conditions, it is probable that correlation of results expressed in this way for the whole human age range would lead to the discovery of an underlying regularity among the results It is tempting to speculate further on the meaning of the changes in Probit lines calculated from the present series For instance, there is a suggestion that the rise in susceptibility from the age of 10 years up to 70 years, as judged by the fall in $L A_{50}$ for instance, follows a course similar to that found for the "force of mortality" in studies of vital statistics It is greatly to be hoped that similar studies on large series of burns or other conditions will lead to further investigation of this fundamental relationship between age and resistance to trauma or disease

SUMMARY

- 1 The mortality findings among 794 burned patients treated in hospital by a Burns Unit are reported
- 2 The importance of the age of the patient and the extent of the body surface area burned in determining mortality is demonstrated
- 3 The analysis of these findings by the Probit technic is explained, and the results of this analysis for separate age groups are given
- 4 The results by age-groups are graphically correlated to show the expected mortality for any given age and area
- 5 A grid table is provided for making a simple comparative assessment of the results obtained in other series
- 6 Similar analyses for conditions other than burns are suggested, and the likelihood of finding a general "law of ageing" discussed

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THE SURGERY OF PATENT DUCTUS ARTERIOSUS*

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SINCE GROSS¹ first successfully ligated a patent ductus arteriosus ten years ago, a large series of operations to stop the shunt of blood from the aorta to the pulmonary artery have been reported from various clinics and much has been learned from them. My discussion will be limited to operative problems and pitfalls in an attempt to present some rational approach to their solution.

INDICATIONS FOR SURGERY

In formulating an opinion as to the advisability of surgery in a patient with an uncomplicated patent ductus arteriosus one must consider the chances of the development of complications in the untreated case and the dangers of surgical treatment. We believe that our experience with 125 patients treated surgically justifies our advising operation on all patients with this lesion except those older than 25 years of age, and those who have no progressive cardiac hypertrophy or incapacitation by virtue of having had a fistulous shunt for so long. We believe the optimum age to be three or four years, although we have operated on a few who have been younger than two years. The older the individual, in our experience, the more difficult is the operation technically. The vessels of young patients are far more elastic and their tissues dissect with much greater ease than those of the older group. Patent ductus arteriosus complicated by subacute bacterial endarteritis should be operated on only after prolonged intensive penicillin therapy. We do not believe that a patient apparently cured of subacute bacterial endarteritis by penicillin should be advised not to have surgery. One should assume that the damage done by infection is not eradicated by penicillin, nor does such an "apparent penicillin cure" necessarily prevent a recurrence of subacute bacterial endarteritis. The fact remains that the presence of a shunt throws a burden on the heart so that the majority of these patients develop a cardiac hypertrophy. Furthermore, dividing and suturing a ductus not only prevents the re-establishment of the shunt, but it also offers greater assurance against recurrence of a subacute bacterial endarteritis.

In young individuals there is no way of predicting with certainty which one will develop cardiac hypertrophy or subacute bacterial endarteritis and so long as the surgical morbidity and mortality rate can be kept very low, we believe that it is urgent to treat these patients surgically before they develop complications.

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DEVELOPMENT OF THE OPERATIVE TECHNIC

It would be well to review the advances that have been made in the technic of the surgery of patent ductus arteriosus in the past ten years. In Gross' original communications^{1, 2} he ligated the ductus "in continuity" with No. 8 braided silk, the technic which we followed in our first few operations. In our third case, previously reported,^{3, 4} the patient unfortunately developed staphylococcus aureus bacteremia and endarteritis some 30 days after operation, and died 48 days postoperatively. Autopsy revealed bacterial endarteritis of the ductus arteriosus and adjacent pulmonary artery, a mycotic aneurysm of the ductus with re-establishment of the communication between the aorta and the ductus. The two ligatures of No. 8 braided silk were lying partially in the lumen of the communication stream. It was obvious that a vessel the size of a patent ductus arteriosus would require a non-absorbable ligature of heavier caliber in order to insure against cutting through the wall of the vessel. The observations of Ballance,⁵ Halsted⁶ and Reid⁷ established that ligatures for large arteries must be of sufficient size in relation to the caliber of the vessel to avoid cutting through the wall. The ligatures must be sufficiently tight to approximate the intimal surfaces and obliterate the stream of blood and not tight enough to fracture the intimal or medial coats. The non-absorbable ligature must not produce enough surrounding fibrosis to involve the recurrent laryngeal nerve in the scar. We therefore resorted to woven silk umbilical tape which seemed to us at the time to be the best material with which to ligate a ductus arteriosus "in continuity," realizing that according to Halsted and Reid, no ligation "in continuity" is foolproof.

Gross⁸ in 1940, apparently believing he could be more certain of obliterating the ductus arteriosus, described his technic of double ligature of braided silk and injection of a sclerosing agent in the segment of the ductus between the two ligatures. Subsequently Gross⁹ described a technic of wrapping the ductus with a band of cellophane about the injected segment of the vessel which lies between the two ligatures in order to combine the effect of the ligation and obliteration by chemical irritation. This latter method he abandoned after several cases.

Frequent changes in the technic for ligation of the ductus arteriosus among various surgeons engaged in this problem is good evidence that they have not been satisfied with the operation and its results. Ligation "in continuity" of a vessel the size of the ductus is fraught with disappointment and sometimes disaster. The persistence or the reappearance of a continuous murmur indicating re-establishment of a fistula are embarrassing complications both to the surgeon and the cardiologist who recommended the operation. The occurrence of a false aneurysm and bacterial endarteritis as the result of the ligature cutting through the wall of the ductus is disastrous and a distinct possibility no matter how meticulously the surgeon has carried out the ligation, for there is no way of being sure that the wall of the vessel is not fractured by the ligature.

In 1944 Gross¹⁰ first described a procedure which might eliminate these problems by dividing the ductus and suturing the divided ends with fine silk. Thus was minimized the danger of recurrent fistulas, aneurysms at the site of ligation, subacute bacterial endarteritis, recurrent laryngeal nerve paralysis by the pressure of and reaction about the tape ligatures and other complications. In his hands this technic has been eminently successful with an extremely low mortality rate. Later Gross¹¹ reported that he had four surgical deaths in 180 individuals treated by the complete division of the patent ductus arteriosus, none of which were directly attributable to the division of the patent ductus itself. In a recent communication Doctor Gross told me he has divided 267 ducti with five deaths, none of which were attributable to the division technic. Since division had not carried a higher operative risk than ligation "in continuity," and since the results were far better, he reported that he had entirely abandoned the procedure of ligation "in continuity."

Blalock,¹² having divided several ducti, decided the technic was too hazardous from the standpoint of a possible hemorrhage and he returned to the procedure of ligation, describing a technic of his own. He tied two purse string sutures of medium silk as close as possible to the aorta and the pulmonary artery, then two mattress sutures were placed between these purse string ligatures. Next, an umbilical tape ligature was tied either between or over these last two centrally placed ligatures. He reported his belief that the results have been as good as with the division technic and that the hazards of hemorrhage are eliminated.

Crafoord¹³ described a technic which he developed by accident as the result of a hemorrhage from a tear in the ductus during its dissection. He placed clamps across the aorta, one above and one below the ductus, and a third on the ductus itself as close as possible to the side of the pulmonary artery, then he divided the ductus at the wall of the aorta. In this fashion he was able to suture the opening in the wall of the aorta and the cuff of ductus distal to the single ductus clamp and accomplish the division of the ductus without the danger of uncontrollable hemorrhage. He has now employed this technic in a large series of cases with no deaths attributable to the division of the ductus. In *none* has there been spinal cord complications as the result of the clamping of the aorta.

Early in 1947 Conklin¹⁴ suggested to me the possibility of using a Potts aortic clamp on the aortic side of the ductus and a Crile clamp or a similar clamp on the pulmonary end of the ductus, then dividing the ductus between the two clamps. The Potts aortic clamp allows a normal flow of blood through the lumen of the aorta. This method certainly eliminates some of the hazards of hemorrhage from slipping of the clamp although in our experience we have never had the clamp slip off the ductus during or after the division of the ductus arteriosus. It seemed to us however that the technic of controlling the aortic end of the ductus with a Potts aortic clamp would be particularly useful in an extremely short, wide ductus and in older patients whose vessels

have not the elasticity that we find in children's vessels. In individuals with sclerosis of the aorta at its junction with the patent ductus arteriosus there is always a potential hazard of a tear at this point either during the dissection of the ductus or after the clamps are applied to divide the vessel. In view of this fact we first mobilize the aorta freely at the site of the ductus and then apply the Potts aortic clamp before completely dissecting the ductus, lest the latter be torn. Thus we eliminate the dangers of a hemorrhage during dissection of the ductus, often necessitating hasty clamping of the aorta and possible injury of the recurrent laryngeal nerve. Then, after a sufficient length of the ductus is dissected, we apply the Crile clamp or the new Potts ductus clamp, divide the vessels between the clamps and suture the open cuffs distal to the clamps.

Recently Potts¹⁵ has devised an ingenious ductus clamp with fine toothlike serrations that will neither injure nor slip off the vessel after its division. The side of the clamp is grooved so that it may be applied on the side wall of the pulmonary artery and aorta, affording greater length of the vessel between the clamps and a longer cuff distal to the clamps for a most satisfactory suture line. The use of two Potts ductus clamps for division and suture of the ductus has the advantage that the clamps cannot crush tissue and, if the ductus is properly dissected before their application, the clamps will not slip or slide off.

COMPLICATIONS

The serious complications that may result from operations on a patent ductus arteriosus should be considered before presenting methods of dealing with operative problems. In our previous communications^{3, 4, 16, 17} we reviewed all of the complications in the first 100 patients operated on for patency of the ductus arteriosus. Only the significant and important complications will be discussed.

Subacute bacterial endarteritis has occurred twice in our present series of 125 cases which have been operated upon. The third patient in the series, who was operated upon in 1939, developed a staphylococcus aureus bacteremia after discharge from the hospital and died 48 days after ligation of the ductus. The source of the infection was never determined but a mycotic aneurysm at the site of the ligation and endarteritis of the pulmonary artery were the cause of death. We were of the opinion that the method of ligation was actually to blame for this complication, but we believed that the blood stream infection probably developed after the fistula had become re-established. However, a few months ago, since our last publications,^{16, 17} a 22-month-old child with a large heart and a patent ductus arteriosus was operated upon most uneventfully by division and suture technic. A few days later she became febrile, a mediastinal mass was diagnosed as a hematoma and several positive blood cultures of staphylococcus aureus were obtained. The patient expired from hemorrhage a few days following mediastinotomy for removal of the blood clot. Sulphonamides, penicillin and streptomycin did not influence the

downhill course Autopsy revealed a subacute bacterial endarteritis in the pulmonary artery, a leak at the site of the pulmonary artery suture and microscopic pulmonary abscesses, but no fistula could be found The source of infection was never established Either the patient already had a latent blood stream infection at the time of operation or the arterial sutures were contaminated No gross pus was found at autopsy and the pulmonary abscesses were all microscopic It seems paradoxical that subacute bacterial endarteritis should occur following an operation that is designed to prevent just such a complication, and that it may occur whether the ductus is ligated or divided We do not believe, however, that a 2 per cent chance of this complication is an argument against operation

A *fistula* between the aorta and a bronchus with large hemoptyses occurred twice, both the result of erosion of knots of umbilical tape into the aorta on the one side and the lung on the other One child was explored, both knots removed, the openings in the aorta and bronchus sutured and she made a complete recovery and is well five years later The other patient, a 42-year-old housewife, still has occasional small hemoptyses though she has gone as long as two and one-half years free of symptoms referable to this complication The use of heavy non-absorbable ligature without closure of the mediastinal pleura over the site of the ductus ligation makes this complication a distinct possibility

Hemorrhage from a tear in the ductus has occurred four times and always during the dissection of the ductus itself In the first patient the tear was small and was easily controlled by the ligatures The second patient had a larger tear requiring the application of clamps and division of the ductus After suturing the two ends of the ductus and having removed the clamps, cardiac arrest complicated the problem and we were unable to resuscitate the heart At autopsy this patient had sclerosis of the ductus and active rheumatic heart disease This year, since our last report,¹⁷ we have torn the ductus at its sclerotic junction with the aorta in two husky 13- and 14-year-old boys The tears were moderate in size but the hemorrhage was insignificant because, with finger compression during the application of clamps to the aorta and pulmonary artery, hemostasis was almost complete Having clamps on the aorta above and below the ductus and a third clamp on the pulmonary artery end of the ductus, the latter was divided and sutured without further loss of blood From both patients we removed tissue at the site of the tear for microscopic study and in each instance sclerosis and vegetations were reported by the pathologist in spite of the fact that we had no history of the patient having had subacute bacterial endarteritis and the patients were entirely afebrile preoperatively so far as we could determine Several postoperative blood cultures were negative and they have subsequently had no complications referable to the ductus itself One of the patients made an uneventful convalescence but the other had a paraplegia immediately following the operation and while he has shown considerable improvement, the obvious residual that he has at present indicates that even a fair recovery is improbable The aorta

had been occluded for approximately 35 minutes, too long a period. The judicious employment of Potts aortic clamp after the hemorrhage had been brought under control would doubtless have avoided this complication of anoxia of the spinal cord.

Since all four hemorrhages occurred during the dissection of the ductus, the hemorrhages were not due to the method of obliteration of the fistula (*i e*, division of the ductus), for indeed, in three patients, it was necessary to divide the ductus in order to close the shunt after the clamps were applied to control the hemorrhage. We have concluded that before any dissection of the ductus itself is undertaken the aorta above and below the ductus should be freely mobilized, so that in the event of a tear of the ductus during its dissection, finger compression at the leak and the application of the Potts aortic clamps will readily allow further dissection of the ductus, as well as application of a Potts ductus clamp on the pulmonary artery end of the ductus and the division of the vessel for suture. The use of the Potts aortic clamp, which allows a normal stream of blood to course through the vessel, reassures the surgeon that he need not hurry the remaining dissection or sacrifice meticulous technic. We had been influenced by Crafoord's¹³ perfect record in his large series of cases where he doubly clamped the aorta during the course of his usual operation for the division of the ductus arteriosus. In retrospect it would have been both judicious and easy to have applied the Potts clamp after controlling the aorta bleeding with Crafoord clamps above and below the ductus.

One other death, the fourth in 125 patients, occurred recently. A two-year-old boy, who had an uncomplicated division of the ductus, developed an acute bronchitis with very thick mucopurulent secretions and died of anoxia 24 hours after operation. Shortly before death the larynx was visualized with a laryngoscope and had a normal appearance, and no secretions were seen in the upper trachea. Autopsy revealed the bronchi to be full of tenacious mucus, the operative field to be without pathological findings and a normal heart. He had had penicillin for 48 hours before surgery and up until his death.

Approximately 25 per cent of the patients developed pleural effusions large enough to warrant needle aspiration. Two patients had postoperative empyema which were cured by rib resection and drainage. There were no wound infections in the entire series. Five patients had a transient pulmonary atelectasis.

Recurrent laryngeal nerve paralysis may occur as the result of operative injury to the nerve or as the result of reaction and scar tissue about the ligatures in close proximity to the nerve. We had three recurrent laryngeal nerve paralysees following the ligations which we believed were due either to trauma or to irritation from the knot. One of these patients has recovered entirely. The other two have permanent recurrent laryngeal nerve paralysis.

In the 58 ligations "in continuity" there were five patients (8.6 per cent) in whom a continuous murmur was noted within the first few days after

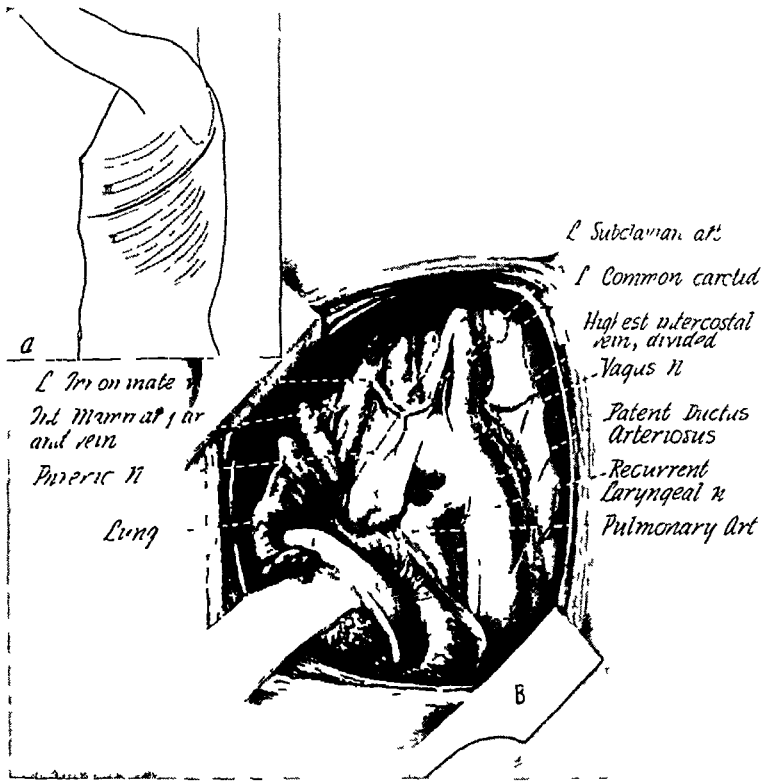


FIG 1 (A and B)—The exposure is obtained through a posterolateral incision and resection of the left fourth rib. Rib spreaders are applied and the mediastinal pleura opened widely for adequate exposure and a thorough anatomical dissection of the mediastinal structures.

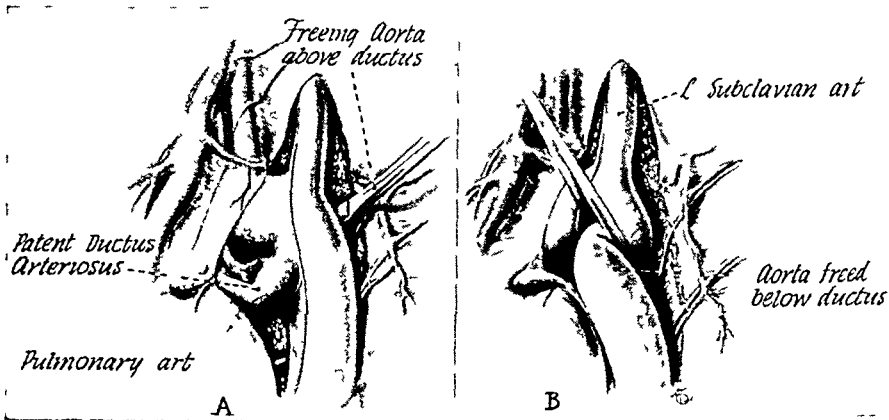


FIG 2 (A)—The aorta is mobilized both proximal and distal to the ductus arteriosus before dissection of the latter is attempted.

(B) Tapes or small Penrose drains are passed around the aorta above and below the ductus and with gentle traction on these, the ductus is carefully dissected to gain its full length for the division technic. Hemorrhage, if encountered, is easily controlled when these precautionary steps are employed.

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operation, and thus we attributed to failure to tie the ligatures tightly enough to occlude completely the lumen of the ductus. Five others (86 per cent) were discharged from the hospital without a continuous murmur but returned in five or six weeks for examination and were found to have a recurrence of the continuous murmur and some even had a palpable thrill. Nine of these ten patients are alive, in seven of them we believe the murmur has decreased in its intensity and is not as loud as before operation and their pulse pressures are lower than before operation.

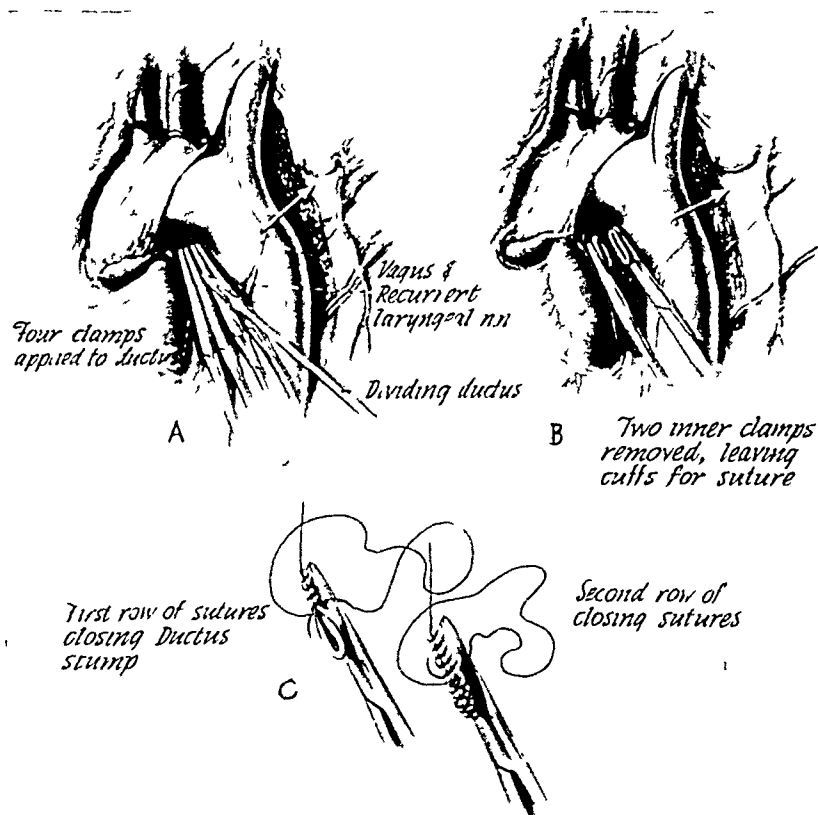


FIG 3 (A)—Four clamps are applied across the ductus arteriosus and the latter is divided with the scalpel after the method of Gross. The vagus and recurrent laryngeal nerves are allowed to retract medially or laterally, whichever way they incline after the dissection. Usually these nerves incline medially or anteriorly as seen in Fig 4.

(B) The two inner clamps are removed for the suturing of the distal cuffs of the vessel. The division between two Potts ductus clamps is carried out if the ductus is short for four clamps.

(C) The cuffs of the ductus are sutured with a running 5-0 silk on an atraumatic needle as previously described by Gross.

RESULTS

Of the 125 patients operated upon (58 ligations and 67 divisions) 121 are alive. One hundred and nineteen patients are well. One patient has a partial paraplegia and one patient (ligation), a diabetic with a persistent fistula, has a low physical reserve, although she has never been decompensated. Eight other patients, all ligations "in continuity" have residual murmurs but are well.

and in seven of these their murmurs are not as loud or as marked as they were before operation. Four patients have a persistent recurrent laryngeal nerve paralysis, though the character of voice has improved with time. There were four deaths due to (1) subacute bacterial endarteritis and aneurysm after ligation, (2) cardiac arrest following hemorrhage at operation, (3) subacute bacterial endarteritis after division of the ductus and, (4) acute purulent bronchitis 24 hours after operation.

DISCUSSION

After reviewing the complications and results of 58 ligations and 67 divisions of patent ductus arteriosus one may evaluate the advantages and disadvantages of the various procedures that have been advocated for the

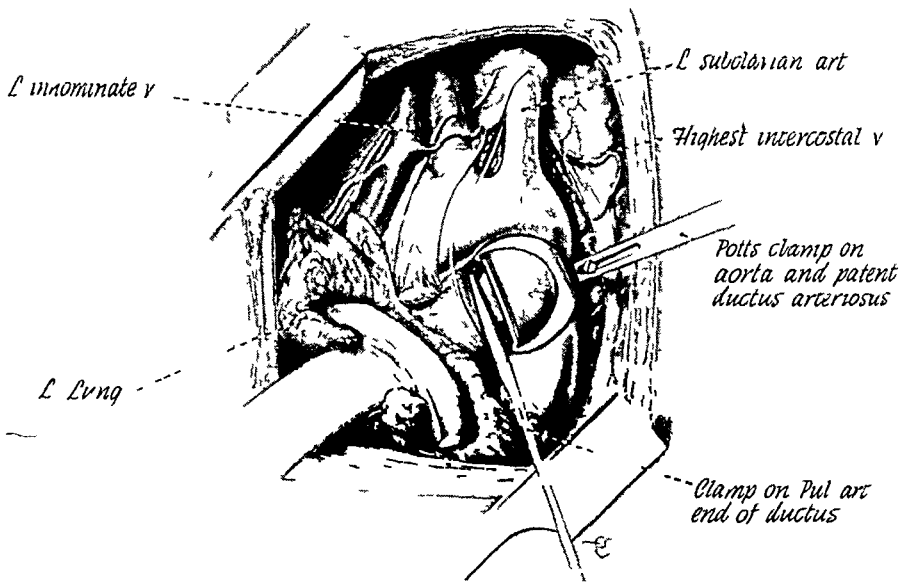


FIG 4—In the presence of a very short and wide ductus one may be forced to apply the Potts aorta clamp and either a single Crile or Potts ductus clamp in order to carry out the division of the ductus with safety. Note the vagus and recurrent laryngeal nerves must be retracted medially. The divided ends of the ductus are closed with a single running stitch of 5-0 silk on a swaged needle.

eradication of the shunt from the aorta to the pulmonary artery. While no one technic may be said to be "the universally ideal operation" certain phases of this surgical problem are worthy of consideration at this time.

1 *The Surgical Approach and Exposure* After we had ligated 41 ducts through the anterolateral approach we turned to the posterolateral exposure resecting the fourth rib, and the latter has been so satisfactory that we have never returned to our former approach (Figs 1A and 1B). The exposure is better, there is more room in which to work, and if hemorrhage should ensue, it can be controlled more easily because of the increased exposure and accessibility of the aorta.

SURGERY OF PATENT DUCTUS ARTERIOSUS

2 *The Mobilization of the Aorta* The mediastinal pleura over the lower subclavian and the aorta should be incised and reflected widely to expose the aorta well above and below the left arch. The highest intercostal vein should be doubly ligated and divided. Then the aorta can be freely mobilized mesial to and above the origin of the subclavian artery and from well below the ductus

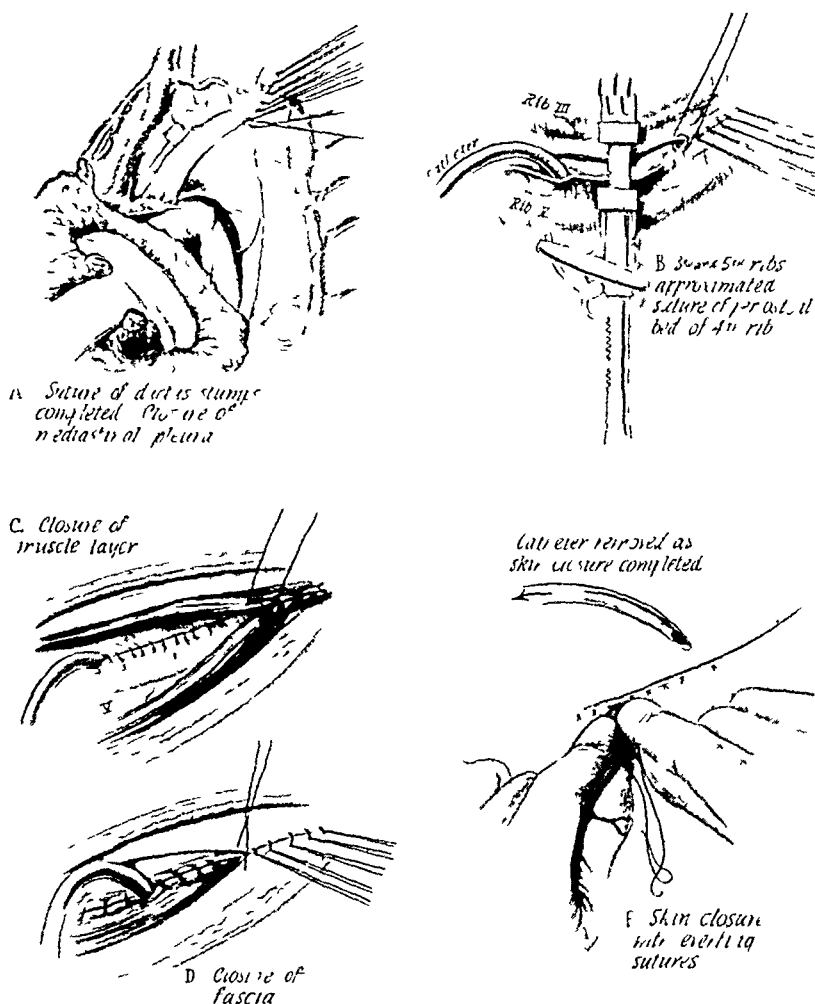


FIG 5 (A)—The suture lines in the pulmonary artery and aorta usually fall about 2 cms apart but in the event they are close together an absorbable sponge is interposed to keep them from rubbing one another. Interrupted fine sutures are used to approximate the mediastinal pleura.

(B) The ribs are approximated with interrupted sutures while a catheter is left in the pleural space for aspiration of the residual air. Positive pressure anesthesia is employed during the chest wall closure.

(C, D and E) The soft tissues are closed in layers and after the skin edges are approximated the pleural catheter is aspirated as it is withdrawn. No pleural drainage is employed.

arteriosus to the upper intercostal arteries (Figs 1A and 2B). Tapes or small Penrose drains are then passed about the aorta below and above the ductus and with these in place the dissection of the ductus may be undertaken with safety. If a tear in the ductus should occur, hemostasis can be obtained at once either with the tapes or by finger compression and the application of the

Potts aortic clamp One can usually identify the bronchial artery during the dissection of the aorta and rarely is it necessary to sacrifice it

3 *The Ductus* In the event that, after the ductus is thoroughly dissected out, it appears that the ductus is too short to place four clamps across it as described by Gross (Figs 3A, 3B and 3C), the surgeon has the option of either applying two Potts ductus clamps high up on the walls of the pulmonary artery and aorta (Fig 3B), or placing the Potts aortic forceps at the ductus and then another forceps on the pulmonary artery end of the ductus (Fig 4) and dividing between the two clamps If the ductus is dissected properly the surgeon should be able to divide even the shortest ductus he may encounter and using these precautions he should have no difficulties in the operation

It would appear that advising the "occasional" operator in this field that he limit his surgery to ligation "in continuity" is not telling him the whole story, for the most likely difficulty he will encounter is hemorrhage during the dissection of the ductus or while he is attempting to pass the ligatures about the ductus Whether the surgeon decides to ligate or to divide the ductus, we would urge him to mobilize the aorta widely before attempting the ductus dissection itself, for then he is master of the situation regardless of hemorrhage The surgeon will soon be convinced that many more ducti are easily divisible after he has followed a safe course of thorough anatomical dissection

SUMMARY

1 Indications for the surgical treatment of patent ductus arteriosus are stated

2 A brief review of the development of the operative technic for the interruption of the shunt of blood from the aorta to the pulmonary artery is presented

3 The postoperative complications and the end results of 125 operations (58 ligations and 67 divisions) for patent ductus arteriosus are reported

4 The rationale of the operative technic we employ in the division of the ductus is given, based upon our own experiences and those of other surgeons

5 Various technics are discussed since the author is of the opinion that at present there is not a "single, universally ideal technic" for the division of a patent ductus arteriosus

6 The importance of adequate exposure and thorough anatomical dissection of the aorta and patent ductus arteriosus is emphasized

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SIGMOIDOVESICAL FISTULAE RESULTING FROM DIVERTICULITIS OF THE SIGMOID COLON*

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DIVERTICULITIS OF THE COLON with its complications presents some of the most difficult surgical problems encountered within the abdomen. Of these complications, fistulae between the sigmoid colon and the urinary bladder are the most perplexing. As has been shown repeatedly, diverticulitis is among the commonest causes of these fistulae. While a great deal of work and writing have been done on the subject, there remains much to be learned about the management of diverticulitis and its complications. The problem presents many controversial points.

The present study consisted of a clinical and pathologic investigation of a number of cases of sigmoidal diverticulitis complicated by the occurrence of sigmoidovesical fistulae. The more important aspects of the subject have been reviewed and elaborated upon.

HISTORY

In 1859, Sidney Jones¹ gave the first accurate report of the necropsy findings in a case of vesicocolonic fistula resulting from diverticulitis. Cripps² in 1888 found that inflammatory lesions more frequently caused sigmoidovesical fistulae than did malignant lesions. Likewise, Heine³ in 1904 and Moynihan⁴ in 1907 realized the importance of diverticulitis as an etiologic factor in these fistulae. In 1907, the work of Mayo, Wilson and Giffin⁵ stimulated much interest in diverticulitis. In two of the early cases reported by them the diverticulitis was complicated by the occurrence of sigmoidovesical fistulae. In 1917, Telling and Gruner⁶ made a very extensive study of diverticulosis and diverticulitis and observed that in 19.8 per cent of the cases reviewed by them, some type of fistula was present.

In 1921, Sutton⁷ concluded from his work that inflammatory disease of the uterine adnexa was the most common cause of sigmoidovesical fistulae and that diverticulitis was the second most common cause. Excellent reports on the subject were given in 1936 by Higgins⁸ and in 1938 by Kellogg.⁹ In 1940, Mayo¹⁰ discussed the surgical treatment of sigmoidovesical fistulae in 54 cases. Diverticulitis was the cause in 32, or 59 per cent. He said that a colic stoma

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placed proximal to the fistula should precede any surgical attack upon the fistula. This opinion was held by Jones¹¹ in 1936, Dixon¹² in 1939, Pemberton³⁰ in 1945 and others. However, Babcock¹³ in 1941 expressed the belief that resection should be done in cases of diverticulitis before the development of fistulae or other complications. Even in the presence of a fistula, he, and frequently Bacon,¹⁴ did a segmental resection and primary anastomosis without colostomy.

MATERIALS AND METHODS

Thirty-two cases of diverticulitis of the sigmoid colon associated with fistulae of the bladder, in which a segment of colon had been removed surgically at the Mayo Clinic, were used for this study. The clinical record in each case was carefully reviewed and abstracted on a specially prepared card. The surgically removed tissues which had been fixed and preserved in formalin solution were examined grossly and roughly sketched. Each specimen was sectioned, and blocks of tissue were removed from selected parts for microscopic study. The blocks of tissue were fixed in paraffin and cut, and the sections were mounted on slides and stained with hematoxylin and eosin. The sections were studied microscopically, and the changes in the various layers of the bowel wall were observed and recorded.

Originally, the clinical records of 40 cases were abstracted, but subsequently the cases in which only colostomy or repair of the fistula had been done and no tissue was available for study were excluded. Of the cases in which surgically removed tissue was available for study, 32 were used. Consequently, this was not a study of 32 consecutive cases of diverticulitis associated with sigmoidovesical fistulae.

The original plan was to study more in detail the fistulous tracts, but in most specimens no tract could be identified. Therefore, in most instances the excised segment of bowel was all that was available for study. According to the surgical note, a segment of bladder was excised in some cases, but in none of the preserved specimens could any bladder mucosa be identified definitely.

PATHOLOGIC FEATURES

In addition to a sigmoidovesical fistula, four patients had other types of fistulae. One had an enterocolic fistula, another had a sigmoidovesicouterocutaneous fistula and two had sigmoidocutaneous fistulae.

The longest segment of colon excised measured 25 cm and the shortest, 7 cm. The average was 12.4 cm. The lumen of the excised segment of bowel had been opened previously in each case.

Gross Appearance—It does not seem necessary nor worth while to describe each specimen separately. In the average specimen, the involved segment of bowel was rigid and thick, with the most markedly involved parts measuring 20 mm or more in thickness, while others were only slightly thicker than the normal of 7 or 8 mm. On the mucosal surface could be seen the diverticular openings, which were multiple in all cases and numerous in most. The mucosa

was thrown into unusually deep folds owing to the contracted underlying bowel wall to which it was fixed. Otherwise, the mucosa was intact in all cases except where perforation had occurred. In most instances only one perforation could be identified, while in some, multiple perforations were present. In two thirds of the cases, perforation was found (Fig 1a).

On the cut surface, the diverticula could be seen penetrating the muscularis or entire bowel wall. They by no means always followed a direct course through the wall, but commonly took a tortuous route or penetrated at various angles.

The submucosa, muscularis and serosa were involved in varying degrees in a chronic proliferative inflammatory process and were, in general, greatly thickened. In some instances, the various layers of the bowel wall could be identified while in others, all the submucosal structures were a mass of scar tissue. The serosal fat was indurated and fibrotic. In some instances, the diverticular sacs could be seen on the serosal surface while in others they were obscured by the overlying fat.

Areas of abscess formation and necrosis were identified in a third of the cases. A definite fistulous tract could be found in only one case.

Microscopic Features—Mucosal ulceration was observed in three-fourths of the cases. This always occurred within a diverticulum, except where the necrotic process extended for a short distance around the offending diverticulum. Where ulceration was present the mucosa was replaced with very inflammatory granulation tissue.

The submucosa, muscularis and serosa were all involved in a chronic proliferative inflammatory process which, in many instances, resulted in replacement of the various coats with dense fibrous connective tissue and granulation tissue, with varying degrees of lymphocytic and plasma cell infiltration (Fig 1b). A few polymorphonuclear leukocytes were present. Hemorrhage was outstanding in some places. Edema was infrequently present. The mucosa overlying the site of such a process was at times intact, the origin of the infection being in a diverticulum which arose some distance away and dissected its way down between and through the layers of the bowel wall. Hyalinization of muscle was present in about half of the cases.

Abscesses were identified in about 50 per cent of the cases (Fig 1c). Most commonly they involved the muscularis and serosa. In none of the cases could mucosal abscesses be seen.

Large multinucleated giant cells of the foreign body type were present in half of the cases. In a few instances, a foreign body granulomatous type of reaction was seen. In a third of the cases, foreign material, which was thought to be contents of the bowel that had entered the bowel wall through the ulcerated areas, was seen. Fat necrosis was prominent in a few instances.

Hypertrophy of the myenteric plexus was present in about a third of the cases (Fig 1d). Generally it was more frequent in those cases in which the proliferative and inflammatory process was most pronounced.

The fistulous tracts all showed essentially the same features. None was lined with epithelium except in those instances in which a long diverticulum itself formed the portion of the tract extending from the bowel to the abscess cavity. The tracts were lined with tufts of very vascular granulation tissue infiltrated

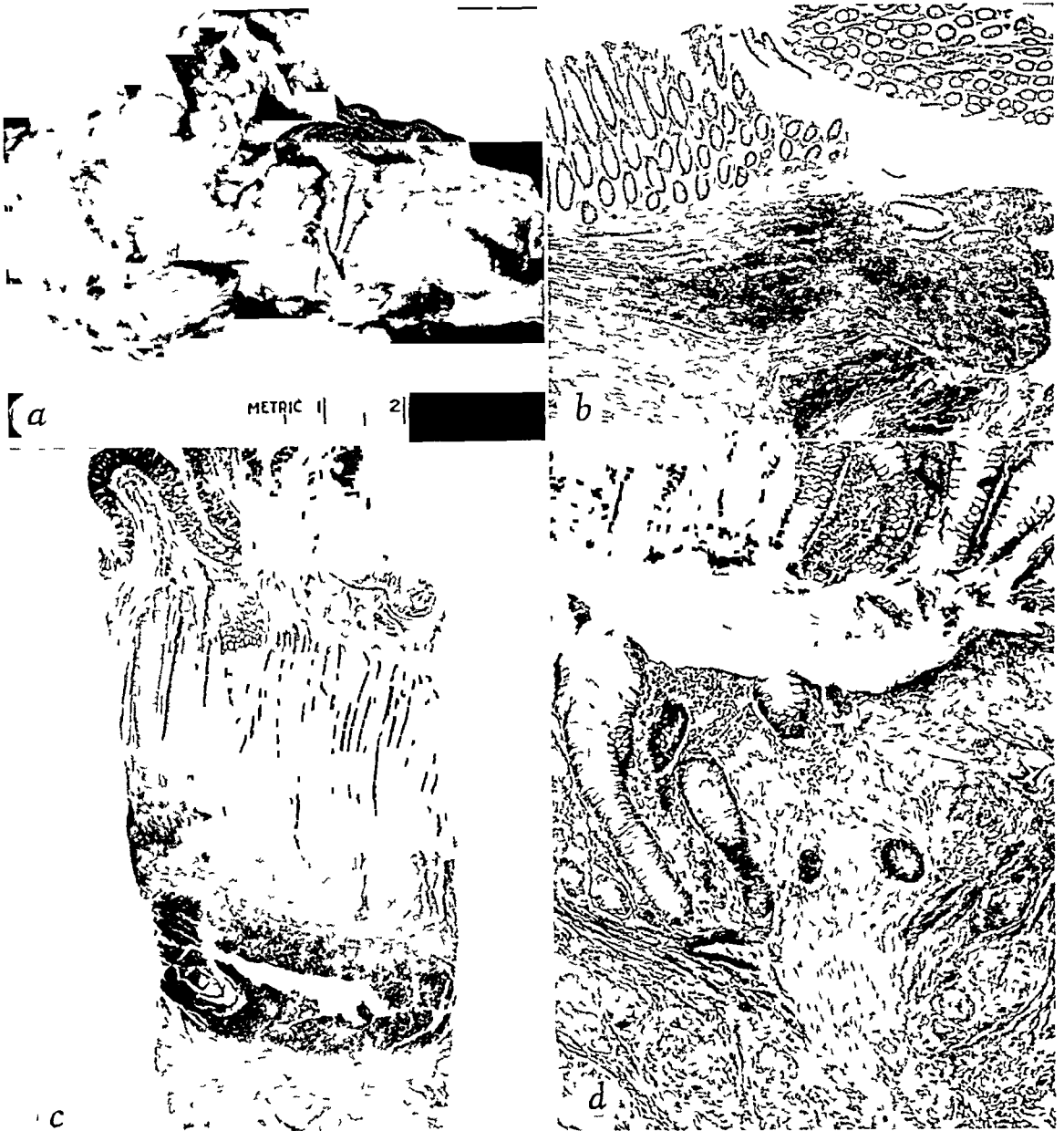


FIG 1 (a)—Perforative diverticulitis of the sigmoid (b)—Perforative diverticulitis of the sigmoid (hematoxylin and eosin $\times 20$) (c)—Abscess between the serosa and muscularis in diverticulitis of the sigmoid (hematoxylin and eosin $\times 47$) (d)—Perforative diverticulitis of the sigmoid with hypertrophy of the myenteric plexus (hematoxylin and eosin $\times 44$)

rather heavily by lymphocytes and plasma cells, especially in the perivascular spaces. Outside the layer of granulation tissue, the tracts were made up of a dense fibrous connective tissue, with varying degrees of inflammatory reaction. Giant cells and small abscesses were observed within the walls of the tracts.

The vascular pattern generally conformed to that described by Lichtman and McDonald¹⁵ in 1944.

An effort was made to compare the gross and microscopic findings in those cases in which a colostomy preceded resection with those cases in which no preliminary colostomy was done. This cannot be expressed well by figures and percentages, but in general, it can be said that the changes were less pronounced if a colostomy had been done six or more months prior to resection. However, in some cases in which colostomy had been done for 12 months or more, perforations, abscesses and necrosis were still present.

CLINICAL FEATURES

Sex and Age—Of the 32 patients who had sigmoidovesical fistulae, 28, or 87.5 per cent, were males. Only four, or 12.5 per cent, were females. The youngest patient was 27 years old and the oldest 76. The average age was 54 years.

Symptoms—Eighteen, or 56.3 per cent, of the patients in this group complained chiefly of symptoms due to disease of the urinary tract. Seven, or 21.9 per cent, had no symptoms referable to the bowel, while in nine, or 28.1 per cent, the symptoms referable to the bowel were most troublesome. Symptoms referable to the urinary tract and those referable to the intestinal tract were equally distressing to five, or 15.6 per cent. Of the abdominal symptoms, pain was the most common, being present in about three-fourths of the cases. Usually it was located in the lower midpart or the left side of the abdomen. Either the bladder or colon could have been responsible for the pain. Constipation was a complaint of a third of the patients. In some the constipation was due to diverticulitis, while in a few others who had been constipated for many years, diverticulitis may not have been the cause. About as many complained of diarrhea. Two patients presented clinical evidence of partial obstruction of the bowel but in none was there complete obstruction. The passage of urine by rectum was an uncommon complaint.

A diagnosis of diverticulitis had been made at the clinic or elsewhere previously in ten cases. The diagnosis was made, on the average, three years before the patients presented themselves at the clinic with fistulae, at which time they had had symptoms referable to the bowel for an average of 4.6 years.

Pneumaturia was the most common and, as a diagnostic aid, the most important symptom referable to the urinary tract. This was a complaint of 30 of the 32 patients. The other two patients had not, to their knowledge, passed gas in the urine, but one had passed barium in the urine after a roentgenologic examination of the colon with the aid of barium. The other patient was found to have a sigmoidovesical fistula when the excised segment of the colon with an attached portion of the bladder was examined by the pathologist at the time of operation. Seventeen passed feces in the urine. Frequency of urination and dysuria were common symptoms. Gross hematuria was present in only a fifth of the cases. Eighteen patients had chills or fever or both.

At the time these patients came to the clinic because of their fistulae, they had had symptoms of disease of the urinary tract for an average of 16.6 months, and they had had their fistulae for an average of 12.9 months. It was considered that the onset of pneumaturia indicated the time of establishment of the communication between the bowel and bladder. In one instance, the urinary tract symptoms and fistula had been present for eight years. The shortest duration of symptoms referable to the urinary tract was two days, and this patient's fistula developed after he came to the clinic.

Previous Surgical Treatment—Twenty-five patients had not had any surgical treatment for diverticulitis before coming to the clinic, seven had been operated upon previously elsewhere. Three patients had had sigmoidovesical fistulae previously. Of these, two had had colostomy, repair of the fistula and subsequent closure of the colic stoma. The third had had a segmental resection of the colon. One patient came to the clinic with a cecal stoma which had been made a year earlier. Two others had had an intra-abdominal suppurative

TABLE I—*Findings on Proctosigmoidoscopic Examination in 28 Cases*

Findings	Cases	
	Number	Per Cent
Diverticula seen	5	17.9
Decreased bowel lumen	8	28.6
Presence of sacculations	9	32.1
Decreased mobility of sigmoid	15	53.6
Negative	4	14.3

process, with surgical drainage. In one case, a segmental resection of the bowel had been done three and a half years previously for a sigmoidocutaneous fistula due to diverticulitis.

Physical Examination—Physical examination revealed the presence of a mass which could be palpated through the abdominal wall in nine cases, by rectal examination in five and by bimanual pelvic examination in one.

Proctosigmoidoscopic examination was done preoperatively in 28 cases (Table I).

Cystoscopic examination was done preoperatively in 25 cases. In 12 cases, the fistulous opening into the bladder was seen, and in 12 others the examiner saw areas in which there were evidence of cystitis, dimpling and projections of granulation tissue, which are findings compatible with the presence of a sigmoidovesical fistula. In one case, a healed fistulous opening was seen. In all 25 cases, immediately after the communication became established there was evidence of acute diffuse cystitis, but later the changes were fairly well localized to the region of the fistulous opening. In some instances, the capacity of the bladder was decreased owing to the presence of scar tissue and contracture of the bladder. The bladder was perforated in various places, but the posterior wall to the left of the midline was most frequently involved.

A preoperative roentgenologic examination of the colon was made in 29 cases (Table II)

The urine was examined in all cases and some degree of pyuria was present in 31. In one case the urine was normal. There was microscopic hematuria in 18. Of 13 cases in which the urine was cultured, *Escherichia coli* was found in 11 and *Shigella* in one, in one case the culture gave negative results.

Treatment Employed—Some type of resection of the colon was done at the clinic at some time in each of the 32 cases, but only 30 of the patients had a resection at the time a sigmoidovesical fistula was present. One patient, whose fistula remained closed after colostomy and subsequent closure of the colic stoma, had a recurrence of diverticulitis and was treated by segmental resection of the colon three years later. In the other patient who had only a repair of his sigmoidovesical fistula, a sigmoidocutaneous fistula developed, for which a resection was done later.

TABLE II—Findings on Roentgenologic Examination of the Colon in 29 Cases of Sigmoidovesical Fistula

Findings	Cases	
	Number	Per cent
Diverticulosis of the sigmoid	6	20.7
Diverticulitis of the sigmoid	18	62.1
Constricting inflammatory lesion of the sigmoid	3	10.3
Obstructing lesion of sigmoid probably carcinoma	1	3.4
Fistulous tract visualized	12	41.4

In 17 instances, or 53.1 per cent of the cases, an extraperitoneal type of resection was done. In eight of these 17 cases a preliminary colostomy was performed. In 12 instances, or 37.5 per cent of the cases, a segmental resection and primary end-to-end anastomosis was done. A preliminary colostomy was done in nine of these 12 cases. One patient came to the clinic with a colic stoma which had been established elsewhere. In this case an ileosigmoidostomy and subtotal colectomy were performed. In six instances, a suprapubic cystostomy was done at the time of resection. In the other cases, a catheter was left in the urethra.

In 19, or 59.4 per cent of the cases colostomy was done preliminary to segmental resection of the colon or repair of the fistula. The colostomy was performed one to 60 months before the secondary procedure, that is, before resection or repair of the fistula, was done. The average time interval elapsing between the two procedures was 15.2 months. In the cases in which both primary and secondary procedures were done at the clinic, the average time interval between the two was 7.5 months.

The continuity of the colon was completely re-established in all except three cases. In one of these, the stoma was said to be 80 per cent closed when last seen.

Results of Treatment—There were three postoperative deaths, giving a mortality rate of 9.3 per cent. In one instance in which an extraperitoneal resection was done ten months after colostomy, the patient died of peritonitis on the fourth postoperative day. The second death, due to peritonitis and pneumonia, occurred eight days after extraperitoneal resection. The third death resulted from gas gangrene after resection and primary end-to-end anastomosis. This patient had a cecal stoma which had been made ten months previously elsewhere.

Of the 29 surviving patients, 28 were cured of their sigmoidovesical fistulae. One patient was said to have a recurrence of the disturbance of the bladder some years later, but information as to whether or not he had a fistula is not available.

Five patients had persistent pyuria, due probably to residual cystitis. It was not thought that they had any infection of the upper part of the urinary tract. Two patients had postoperative sigmoidocutaneous fistulae, one of these fistulae followed simple repair of the fistula of the bladder, but later it was cured after segmental resection of the colon. Two patients are known to have had a recurrence of diverticulitis. One committed suicide, and the second, whose fistula of the bladder closed spontaneously after establishment of a colic stoma which was also closed after 20 months, remained well after a segmental resection of the colon was done three years later.

COMMENT

Diverticula of the colon occur most commonly in people above 40 years of age. Males are affected more often than females, the ratio being about 3:2. The pelvic colon is most often the site of involvement, and by far the majority of complications resulting from diverticula occur in the sigmoid. It is not the purpose of this paper to discuss the controversial points regarding the etiology of diverticula. It is the opinion of most authorities that their formation is the result of several factors, the most important of which is increased intraluminal pressure plus weakness in the musculature of the bowel wall produced by the penetration of the wall by blood vessels and possibly fat.

The wall of a diverticulum is composed of atrophic mucosa, submucosa and serosa. Not infrequently, a thin layer of muscle is present, especially near the proximal end of the sac.

Fecal concretions, which are contained within these sacs, cause mucosal erosion and irritation, permitting bacterial invasion of the wall of the sac. The inflammatory process initiated by the invading bacteria and toxins occludes the mouth of the diverticulum and produces necrosis and extension of the process into the adjacent bowel wall. The severity of the inflammation depends upon the virulence of the organism and resistance of the patient.

If the process spreads rapidly, there is necrosis of the diverticulum and bowel wall, perforation and abscess formation. The abscess may attach itself to the abdominal wall, bladder or other viscus and erode through the wall of the viscus producing a fistula.

More commonly, the process spreads more slowly. The wall of the bowel and the mesentery then become involved in a chronic proliferative extramucosal inflammatory process, which Wilson⁵ in 1907 called "peridiverticulitis." This is the most important pathologic condition resulting from diverticula. The involved loops of bowel become attached to the abdominal wall or viscera, and abscesses form within the inflammatory mass from time to time and drain through the path of least resistance. Frequently, this path of drainage is into the colon, but not infrequently it is into the bladder or small bowel, or through the abdominal wall. This seemed to be the mechanism at work in practically all the cases in this present study.

Since this study is not based on a group of consecutive cases of diverticulitis of the sigmoid associated with sigmoidovesical fistula, one cannot, from it, determine the incidence of the disease. It has been shown that 5 to 10 per cent of people who undergo roentgenologic examination of the colon have diverticulosis. According to Brown and Marckley,¹⁶ 12 to 17 per cent of those with diverticula have diverticulitis. From his review of the literature, Arnheim¹⁷ concluded that approximately 8 per cent of those with diverticulitis have a sigmoidovesical fistula. Lett and co-workers¹⁸ and Edwards¹⁹ determined that in 10 per cent of patients with diverticulitis have symptoms of disease of the urinary tract. According to Brown,²⁰ 15 per cent of patients who have surgical treatment for diverticulitis have a sigmoidovesical fistula.

Sutton⁷ found that pelvic inflammatory disease was the most common cause of sigmoidovesical fistula and that diverticulitis was the second most common cause. In his group, 17.6 per cent of the fistulae were due to diverticulitis. Bryan,²¹ David,²² Gaffney,²³ and Higgins⁸ expressed the belief that diverticulitis is the most common cause of sigmoidovesical fistula.

Women much less commonly have sigmoidovesical fistulae than do men, not only because diverticula are more common in men, but also because the uterus and adnexa are situated between the sigmoid and the bladder in most instances. There were only four females in this group, one of whom had undergone hysterectomy several years before a fistula developed and the second of whom had undergone salpingo-oophorectomy previously. The other two had had no previous pelvic operation.

It is interesting that with many of these patients the cardinal symptoms were those of disease of the urinary tract, while their intestinal symptoms were minimal or, indeed, frequently absent. Of the present group, 21.9 per cent had no symptoms referable to the bowel. The development of a sigmoidovesical fistula may, at times, be lifesaving. By it abscesses are drained and obstruction of the bowel may be at least partially relieved. Thus it is not strange that the establishment of a fistula would lessen the severity of the symptoms referable to the bowel.

Obstruction of the bowel seemed to be an important factor in only two of these cases, but had many of these patients been seen during the acute episode of abscess formation and perforation obstruction might have been a more

prominent feature. However, Mayo²⁴ observed that obstruction was usually not present in perforative diverticulitis.

The origin of intestinal bleeding is difficult to determine, and no attempt was made to determine its frequency in the present study. Some of the patients had seen blood in their stools, but in many instances the blood came from hemorrhoids. In no case was bleeding severe.

Pneumaturia and the passage of feces in the urine are positive evidence of the presence of a fistula between the bowel and urinary tract. When a patient presents himself with pneumaturia, there are at least three possibilities according to Kelly and MacCallum²⁵: 1. Air may have been introduced into the bladder from without. 2. The urinary tract may be contaminated by gas-producing bacteria. 3. There may be a communication between the intestinal and urinary tracts. Occasionally, these patients do not volunteer the information that they pass gas in the urine, and only on specific questioning is the information obtained.

Edwards²⁶ found that in his group of 15 cases of sigmoidovesical fistula resulting from diverticulitis, the average duration of abdominal symptoms prior to the establishment of the fistula was three years and nine months, while in our group, it was three years and three months. In our group, the symptoms of disease of the urinary tract were present an average of 3.7 months before positive evidence of a fistula developed, and the fistula had been present an average of 12.9 months when the patient was first seen at the clinic.

In many cases, the onset of symptoms referable to the urinary tract corresponds with an acute episode of abdominal pain and fever. Pyuria may herald the rupture of the abscess, with relief of pain, air and feces may appear in the urine only after the lapse of several days that may be required for the establishment of the sigmoidovesical communication.

As pointed out by various investigators, infection of the upper part of the urinary tract is an infrequent complication, and the ability of the bladder to tolerate the fecal discharge is remarkable, in none of our group did it appear that there was such an infection. Five patients had persistent pyuria after the fistula was closed surgically, but none of these seemed to have an infection of the upper part of the urinary tract.

While the diagnosis of enterovesical fistula is usually not difficult, it is not always simple to determine the etiology and the portion of the bowel involved. From the literature, Higgins⁸ found the etiology in 328 cases of enterovesical fistula to be as follows: congenital causes in 5.7 per cent, trauma in 14.9 per cent, inflammatory processes in 48.4 per cent and neoplasms in 27.7 per cent, of the inflammatory lesions, diverticulitis was the most common offender. Other causes were tuberculosis, appendicitis, vesical calculus, syphilis, diverticulum of the bladder, typhoid, actinomycosis and perianal abscess. Carcinoma of any of the pelvic structures may result in a sigmoidovesical fistula.

Bargen and Cox²⁷ discussed the differential diagnosis of malignant and nonmalignant perforating lesions of the colon. Perforative diverticulitis was

suggested by a history of rather long-continued recurrent pain in the lower left quadrant of the abdomen, with mild obstructive features, sudden pain, a tender, fixed mass in the lower left quadrant and a temperature of 102 degrees F or more. Perforating carcinoma was likely to be a more slowly progressive process, with more marked obstructive features, bleeding, low grade fever and anemia.

Roentgenologic examination of the colon gives the most reliable information as to the nature and location of the lesion responsible for the fistula, but as emphasized by Dixon and Weber,²⁸ when a malignant lesion of the colon perforates, it may very closely resemble diverticulitis. In the present series, a diagnosis of diverticulitis or diverticulosis or both was made in 82.8 per cent of the 29 cases in which roentgenograms were made, in one case the lesion had the appearance of a carcinoma.

Proctosigmoidoscopic examination is important, but rarely with it alone can one make the diagnosis. Usually one can get only suggestive evidence that the disease of the bowel is diverticulitis. The proctoscopic findings of narrowed lumen, immobility, mucosal edema, angulation and extrarectal mass are suggestive but not diagnostic of diverticulitis, as shown by Jackman and Bue.²⁹ At times, the presence and location of the fistula can be determined by placing a solution of methylene blue in the bladder and observing its appearance in the bowel. Also cystograms are at times useful.

From the group of cases in this study, one could not draw conclusions as to the proper method of treatment, since only cases in which resection of the bowel was done were used. However, these fistulae rarely close spontaneously, and it is agreed that the proper treatment is surgical. Pemberton,³⁰ Edwards,¹⁹ Lockhart-Mummery³¹ and others have agreed that multiple stage procedures are preferable. An extraperitoneal type of resection may be done when possible. Frequently, any type of resection should be preceded by establishment of a temporary colic stoma which completely diverts the fecal stream for three to 12 months. Babcock³² has followed the practice of doing a segmental resection and primary anastomosis without a colostomy in perforative diverticulitis.

Some fistulae can be corrected by separation of the bladder and sigmoid and closure of the openings. A colic stoma placed proximal to the fistula and closed after a period of several months will suffice in some cases, but too often the fistula will recur or there will be an exacerbation of the diverticulitis. In this study, an effort was made to determine from the case records if the fistula closed after the colostomy, but this could not be done with any degree of accuracy. When a colostomy is done proximal to the diseased segment of bowel, the inflammatory process subsides somewhat, but not completely, and as the bowel is put to use again the process is reactivated, more abscesses forming and draining through the bladder. Any procedure short of resection frequently fails to correct the fistula, because it does not remove the primary cause of the condition.

In ten cases of this group colostomy and in one case cecostomy had been

done six or more months prior to segmental resection of the sigmoid. In the excised specimens one could see the necrotic, perforated areas in five instances. In six of these 11 cases microscopic and, in some instances, gross abscesses could be seen in the wall of the bowel.

Only five of the resections were done prior to 1939, consequently most of the patients had the benefits of chemotherapy. Approximately half of the patients were prepared preoperatively with the aid of succinylsulfathiazole (sulfasuxidine). The two patients who died of peritonitis, and peritonitis and pneumonia, respectively, were operated upon in 1930 and 1934 when the sulfonamides were not available.

SUMMARY AND CONCLUSIONS

A review of the literature on sigmoidovesical fistulae associated with diverticulitis has been presented. It is the opinion of most investigators that diverticulitis is the most common cause of sigmoidovesical fistulae.

A study based on 32 cases of sigmoidovesical fistula due to diverticulitis of the sigmoid colon was made. In each case, segmental resection of the colon was done at the Mayo Clinic.

Characteristically, the excised segment of the colon presented many diverticula. The wall of the bowel was involved in a chronic extramucosal proliferative inflammatory process. Commonly, areas of necrosis, abscess formation and perforation were seen.

As with colonic diverticula, fistulae were more common in older men. Women are much less likely than men to have sigmoidovesical fistulae because of the protection afforded the bladder by the female pelvic viscera.

The symptoms of sigmoidovesical fistula were abdominal pain, constipation, diarrhea, pneumaturia, frequency of urination, dysuria, the passage of feces in the urine, hematuria, the passage of urine by rectum and chills and fever. Either the intestinal or urinary tract symptoms may predominate. The patients had had symptoms of diverticulitis an average of approximately 3.5 years and their urinary tract symptoms an average of approximately 3.5 months when their fistulae developed. Most of these fistulae developed spontaneously.

Cystoscopic examination and roentgenologic examination of the colon were the most important aids in the diagnosis. Other inflammatory lesions and carcinoma must be considered in the differential diagnosis.

Infection of the upper part of the urinary tract is not a common complication of sigmoidovesical fistula, and it was not present in any of our cases.

Spontaneous closure of the fistula is rare. Any type of surgical treatment less radical than excision of the diseased segment of colon and closure of the vesical opening usually fails. In most instances it is advisable to provide proximal drainage by means of a temporary transverse colostomy for six months prior to resection. In this group of 32 cases, there were three postoperative deaths. Twenty-eight were relieved of their sigmoidovesical fistulae.

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INTUSSUSCEPTION IN INFANTS AND CHILDREN*

A REPORT OF 143 CONSECUTIVE CASES

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The progress of medicine and surgery in lowering the mortality of acute intussusception in infants and children has been slow. An analysis of the results obtained in 143 cases at Children's Hospital, Los Angeles, during the last ten years has shown real progress as compared with comparable series reported in the literature (Table I). Reasons for this improvement seem apparent, and these, plus the lessons learned from our own unsuccessful cases, have prompted us to present this report.

DIAGNOSIS

Credit is due the pediatricians who referred these cases for hospitalization in the early stages of the disease. The average duration of symptoms before surgery was performed was 28 hours (Table II). Ladd and Gross reported 30 hours¹³, Robbins 45 hours²¹, Peterson and Carter, 32 hours¹⁹, Gibbs and Sutton, 47.5 hours⁸ and Gordon, 36 hours¹⁰.

Intussusception occurred most frequently among well-nourished, apparently well infants between the ages of four and nine months (Fig 1). Sixty-three per cent of our cases were males and 37 per cent females. The onset of symptoms was usually abrupt, with intermittent attacks of severe abdominal pain, lasting a few minutes and followed by a free interval of from 15 to 20 minutes, in which the child appeared perfectly well. Often the attack of pain was of such severity as to cause the child to become pale and show temporary signs of shock. The attacks of pain were frequently followed by nausea and vomiting, and in 55 per cent of the cases, with bloody stools. An abdominal mass was palpated in 69 per cent. Roentgenograms of the abdomen or barium enemas were taken in 22 per cent. They are occasionally helpful when the diagnosis is in doubt and barium enemas are at times even curative but may be misleading if the intussusception does not involve the colon. This situation occurred in four of our cases.

DIFFERENTIAL DIAGNOSIS

The important conditions which must be recognized in the differential diagnosis are intestinal colics which are not accompanied by mechanical obstruction. Henoch's purpura should also be added to this list. We recently had a classic example of this combination of medical and surgical conditions

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TABLE I—*A Comparison of the Mortality Rates in Some of the Reported Series of Cases of Intussusception in Infants and Children*

Authors	Institution	Periods of Observation	Number of Cases	Mortality Percentage
Perrin and Lindsay ¹⁷	London Hospital Children's Div	1903-08	138	49.2
		1909-14	149	27.5
		1915-20	113	26.6
			400	34.75
Close ⁵	Guy's Hospital, London	1904-16	131	40.0
		1919-27	106	20.6
			237	35.4
Brown ⁴ Robins ²⁰	Philadelphia Children's Hospital	1915-24	31	64.5
		1924-31	34	35.3
			65	49.2
Clubbe ⁶ Hipsley ¹¹	Sidney Australia Children's Hospital	1921	144	32.0
		1937	142	4.9
			286	19.0
Ladd and Gross ¹³	Boston Children's Hospital	1908-27	282	37.0
		1928-32	90	14.0
		1933-39	112	12.5
			484	26.9
Nyborg ¹⁵	Kronprinsessen Louisa's Vardanstalt Stockholm	1930-34	24	17.0
		1935-41	84	5.0
			108	7.3
Gibbs and Sutton ⁸	Cincinnati General Children's Hospital	1927-37	56	44.6
		1937-42	36	8.3
			92	30.4
Musil ¹⁴	Children's Memorial Hospital Chicago	1933-43	105	16.1
Bolling ³ Hogg and Donovan ¹²	Babies Hospital New York	1923	50	30.0
		1927-45	123	13.0
			173	21.3
Oberhelman and Condon ¹⁶	Cook County Children's Hospital Chicago	1925-31	13	53.8
		1932-38	18	16.6
		1939-45	68	13.2
			99	19.1
Snyder Kraus and Chaffin	Children's Hospital Los Angeles	1938-48	143	4.8

in an 8-year-old girl, not included in this series. The purpuric spots, the fretfulness and generalized irritability delayed our recognition of the acute intussusception until 12 hours after her admission to the hospital, but following resection of the gangrenous loops, the child made an uneventful recovery. Gastritis, enterocolitis, allergic states and mesenteric enteritis may produce a picture which closely simulates intussusception, furthermore, cases do reduce spontaneously,⁹ or with ordinary or barium enemas^{1, 20, 22}. In our series there were 18 cases in which the signs and symptoms, and occasionally the barium

TABLE II—*Duration of Symptoms*

Hours	Number of Cases
0 to 6	32
7 to 12	31
13 to 24	33
25 to 48	22
49 to 72	10
96	7
Over 96	5

enema, made the diagnosis of intussusception seem likely, yet the findings were not definite and considered judgment favored a period of observation. Sixteen of these cases entirely cleared and were sent home well and without operative intervention. In two, after nearly 72 hours' observation, operation was performed with recovery in both instances. A quotation from the notes of Dr. Joseph Brennemann, written in 1942 on one of our patients who was observed and who recovered without operation, is as follows: "I cannot make

AGE INCIDENCE

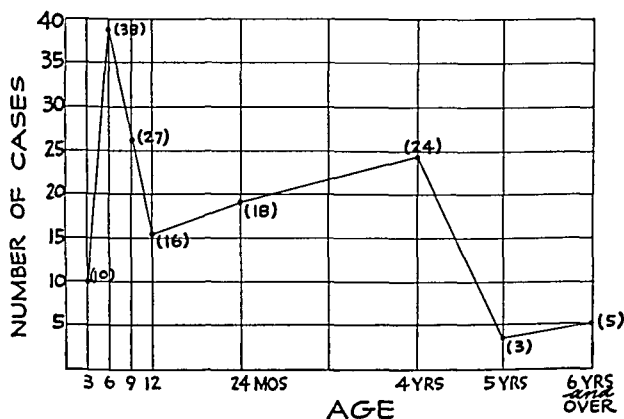


FIG. 1

out a mass, and there is no mass on examining the rectum. The rectum does not have the empty feeling. If it is an intussusception, it is not a 'tight' affair and one can safely wait. Since he came in three or four hours ago, he has had practically no tenderness. He should be watched carefully." In two cases the abdomen was opened and no evidence of past or present intussusception was found. The differential diagnosis was difficult in 15 per cent of our series.

CLASSIFICATION

It is important to remember that intussusception may involve only the small intestine and that a barium enema in this type cannot be helpful and may be actually misleading. All our cases, with four exceptions, involved the colon. For practical purposes, we have not carried this classification any further.

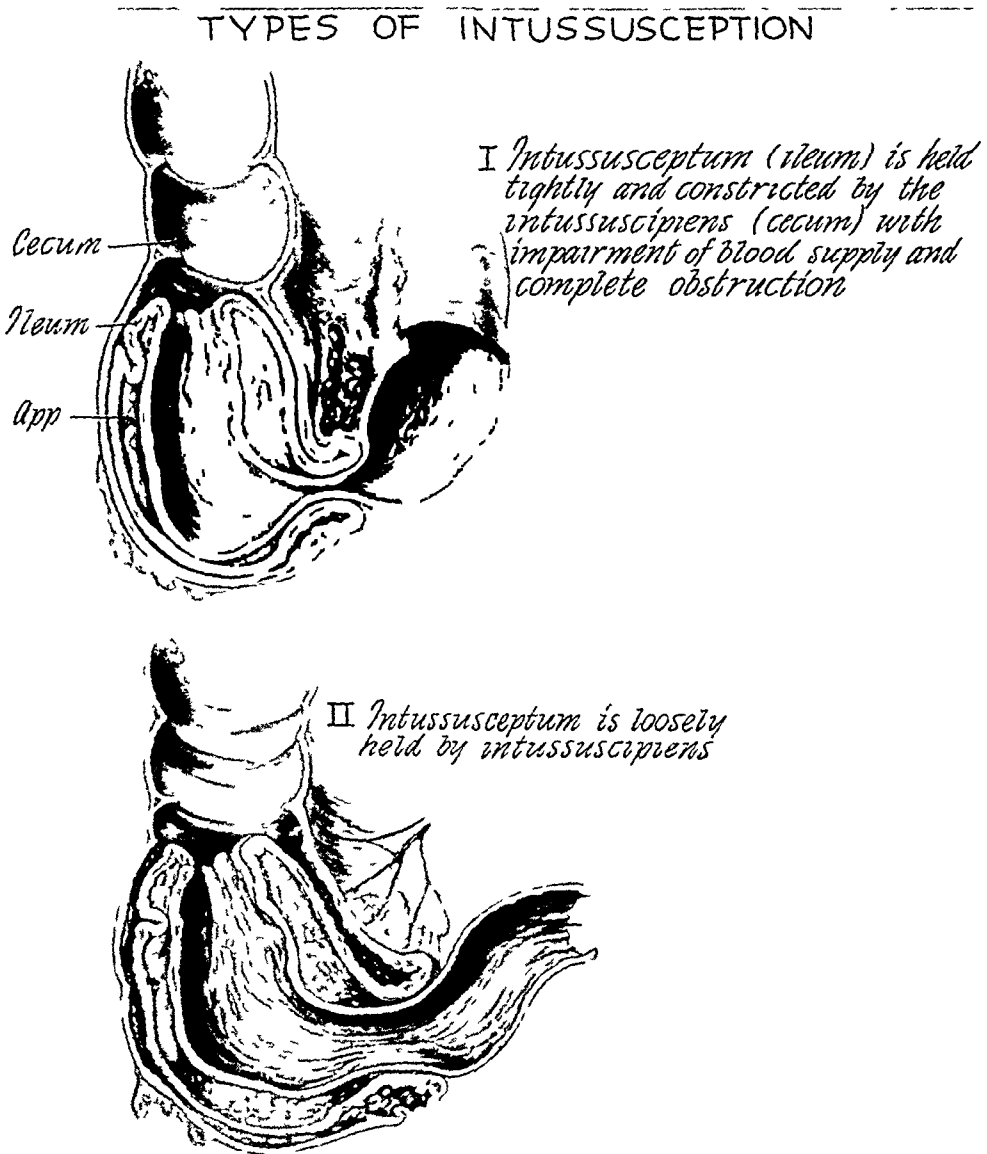


FIG 2

From a clinical standpoint, however, we recognize two types of intussusception. Fig 2, Type I, in which the intussusceptum is tightly held by the intussuscipiens, causing interference with blood supply and complete obstruction, and Type II, in which the intussusceptum is loosely held and, therefore at first causes only partial obstruction and little vascular damage (See Fig 3). This is a pathologic classification and is definitely determined only at operation. It does, however, explain why some cases (three in our series) have a gan-

genuous loop only 24 hours after the onset of symptoms and many cases (12 in our series) may go as long as three days or more without any real damage to the intussuscepted intestine. This concept furthermore explains why in some cases the symptoms are milder and evidence of complete obstruction and toxicity are not present even after the first day or two of the disease. It should not, however, be used as any excuse for delay in treatment except when the symptoms, examination and laboratory findings leave the examiner in real doubt as to whether or not he is dealing with an intussusception or with some



*Streptomycin injected proximal to
area of bowel involved in intussusception*

FIG 3

other medical condition in which surgery is not indicated. A barium enema may or may not settle the problem. It is of no value if the intussusception is ileo-ileal. If the barium enema is not positive, then a period of close observation for a few hours is justified.

TREATMENT

The first fundamental principle is the agreement that surgery is indicated when one is reasonably certain that intussusception exists. If the utilization of conservative means of reduction is confined to diagnostic procedures, such as barium enemas, when the signs and symptoms are not clear cut, then

there will be no undue procrastination and the general mortality from the condition can be reduced

The second fundamental principle, which we believe has led to a reduced mortality in this series, is the institution of measures directed toward correcting the alterations of body economy produced by the intussusception. Sixteen surgeons, with varying degrees of experience, operated upon our 125 patients but the standard of preoperative and postoperative care was much the same throughout the series. Intussusception produces (1) low mechanical obstruction with attendant loss of water and electrolytes, (2) blood loss into the bowel and into the damaged tissues, (3) a localized lowering of the defense mechanism against infection. Present methods to combat these alterations have developed in recent years and need only a practical application.

PREOPERATIVE CARE

Intranasal gastric suction is indicated in all cases. This is removed after surgery if postoperative obstruction is not anticipated, or, on the other hand, a Miller-Abbott tube is inserted if obstruction is a major factor. *Water, salt and glucose* are given to those patients who present evidence of having lost these essentials. In 50 per cent of our cases, fluid administration was not felt to be necessary. Blood is given to those patients who are in poor condition. Evidence of shock or toxicity suggests a type I intussusception and the patient needs blood early, 10 cc per pound of body weight is given as an initial amount and is repeated as indicated. Fifteen cases in our series received this form of therapy. *Antibiotics and chemotherapeutic agents* should be administered to the clinically ill patients,² and to those patients who have had a preliminary diarrhea or evidence of other infection, 150,000 units of penicillin (16 cases), and 1 gram of streptomycin (7 cases), per 24 hours, given in divided dosages, have been found to be effective. Sulfadiazine has also been used in 35 of our cases. This was administered as the sodium salt, in divided dosages of 1 grain per pound of body weight per 24 hours, given intramuscularly.

In one-half of our cases, the general condition of the patient was good and no preoperative therapy except aspiration of the stomach seemed indicated. In those patients, who are in poor condition, however, we believe that the few hours taken up in administering fluid, electrolytes, blood and antibiotics are well spent. To rush a gravely ill child to the operating room is, in our opinion, poor judgment. Similarly, to delay surgical relief too long is to court disaster. When the child is in good condition, one hour is ample time, when the child is gravely ill, we feel that three or four hours may well be spent in preparation. The lesson learned as regards pyloric stenosis, when preparation may require from one to four days, might well be condensed to from one to four hours, as applied to intussusception.

OPERATION

Drop-ether anesthesia is used. Blood or plasma is advised during surgery.

if the patient's condition is not good. In one of the two deaths following resection in our series, this was not done. The exposure is usually made through a right-rectus incision. The intussuscepted loop is located and reduced, if possible, by pressure through the distal bowel, against the head of the intussusception. Tension on the proximal bowel is kept minimal. Good judgment is required in determining just how long one can persist in attempting to reduce a tight intussusception, but it may often require from 10 to 15 minutes and will usually be rewarded with success and a viable intestine. In only 4 per cent of our cases was resection necessary, either because the intussusception could not be reduced or the intussusception was gangrenous. When a resection is necessary, or when the intussusception is badly damaged, we favor the introduction of one gram of streptomycin through a small-gauge needle into the loop of small intestine, either proximal to the anastomosis or to the intussusception (Fig 3), along with full parenteral administration of antibiotics. This is, as yet, not based on sufficient clinical experience but on

COMPOSITE TEMPERATURE CURVE
Patients given no antibiotic or chemotherapy

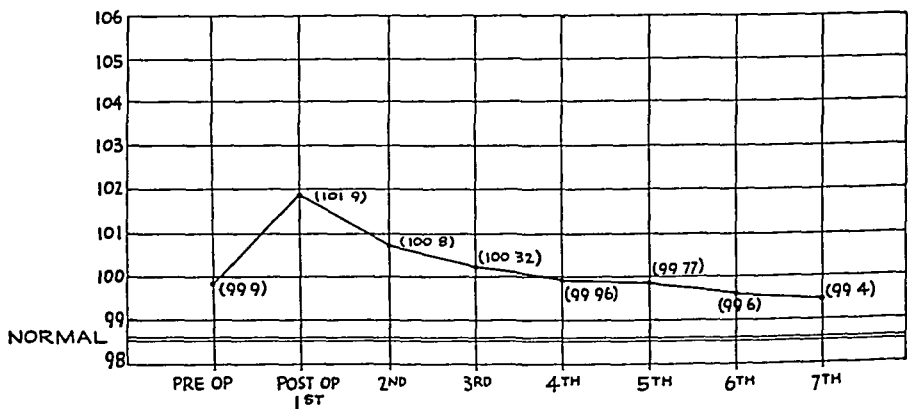


FIG 4

the experimental work of Farris and Romack⁷ and others²⁴. In theory, at least, it should produce a rapid intraluminal sterilization almost akin to that afforded by the "prepared" bowel of elective surgery.

In those cases in which the intussusciens has caused only little damage to the intussusceptum and the child is in good condition, an appendectomy also is performed. There were 24 cases in which this accompanying procedure was done. There were four cases in which a Meckel's diverticulum was removed. No operative procedures were performed for the prevention of recurrence except in a very few cases. It is not recommended.

POSTOPERATIVE CARE

The postoperative course in the cases in which there is little damage to the intussusceptum is accompanied by little reaction (Fig 4). These cases require no special therapy. The stomach tube is removed immediately postoperatively.

The patients are allowed water, liquids and solids as tolerated. Supplemental parenteral fluids are not often administered. In these cases, antibiotics and chemotherapeutic agents are not given unless there has been an antecedent history of diarrhea.

Cases in which a resection has been necessary, or those in which there has been severe damage to the intussusceptum, are given strenuous postoperative care. Constant suction is maintained. Blood (38 cases), plasma, saline and glucose are administered parenterally. Oxygen tents are utilized. Penicillin (24 cases), and streptomycin (7 cases) and sulfadiazine (35 cases) are administered in full therapeutic dosages. Parenteral vitamins are not neglected. In spite of these measures, a stormy convalescence can be anticipated (Fig 5).

COMPOSITE TEMPERATURE CURVE
Patients on antibiotic and chemotherapy.

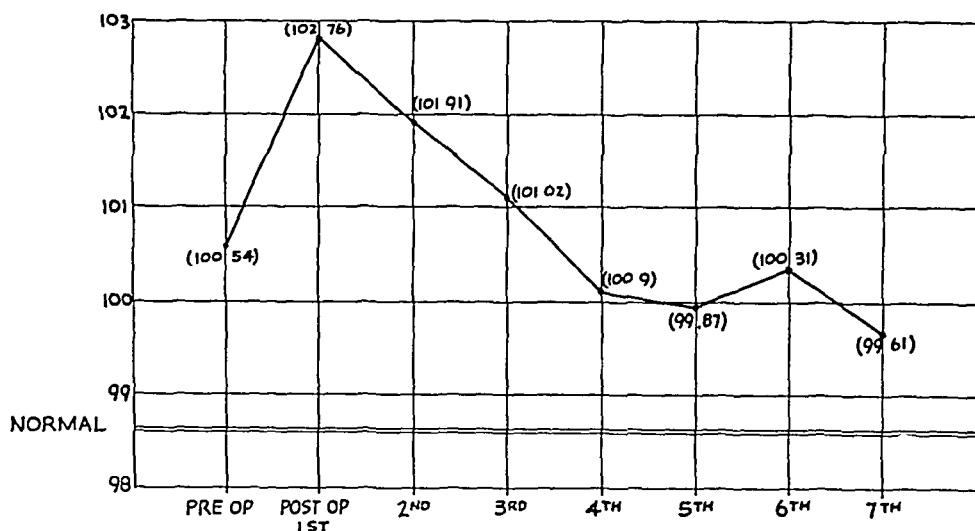


FIG 5

PATHOLOGY

Only 4 of our 125 consecutive operated cases were enteric. The rest involved the colon. In six cases, there was gangrene of the intussusception requiring resection, an incidence of 4 per cent. There were four cases with a Meckel's diverticulum and one with duplication cyst of the ileum.

One death occurred following resection, due to shock in a patient inadequately prepared with fluids and blood. One child died of continued complete intestinal obstruction, after resection and end-to-end anastomosis. This was due to a large cuff at the anastomotic site, as determined at autopsy. The lessons to be learned from these two cases are self-evident. One baby died of a blood-stream infection, with a gram-negative bacillus. This occurred four days following a simple early reduction. In this case, there was a five-day history of watery diarrhea, preceding the onset of the symptoms of intussusception. Perhaps full dosages of antibiotics should be given to this type of case. One infant died with generalized peritonitis following a resection, in

which the intussusceptiens was so friable that it perforated almost when touched. There was one death from bronchopneumonia 18 days after a resection. Two patients expired with a concomitant nonrelated lethal disease, one having a severe cardiac anomaly and the other chronic lymphatic leukemia. A brief synopsis of all deaths is added.

DEATHS

1 A one-year-old child was admitted with a two-day history of abdominal pain and vomiting. The child was stuporous. No fluids were given at operation. An intussusception with gangrenous terminal ileum was reduced but resection could not be carried out because of the child's poor condition. A resection was performed the next day but the child died in shock one hour later.

2 An eight-months-old baby entered with a three-day typical story of pain, vomiting and bloody stool. An abdominal mass was palpated. A nonreducible ileo-ileal intussusception was resected. An aseptic technic with clamps was used and an end-to-end anastomosis completed. The child died three days later with a high temperature and at autopsy complete obstruction was found at the site of the anastomosis.

3 A three-and-one-half-month-old infant was admitted with a history of five days of watery green stools and typical signs of intussusception of five hours' duration. A simple reduction of an ileocolic intussusception was performed. He did well for two days and then developed a high temperature and toxicity. Penicillin was administered. At post-mortem, two days later, gram-negative bacilli were found in the blood stream.

4 A six-and-one-half-months-old child was brought to the hospital with a six-day story of vomiting and bloody diarrhea. At operation, an intussusception extending to the sigmoid was found. The colon was so friable that it perforated almost when touched. The colon and the intussusception were resected and the ileum and sigmoid were brought to the outside. The child died 24 hours later with a generalized peritonitis.

5 A three-months-old baby was seen with a three-day history of vomiting and bloody stools. An ileocolic gangrenous intussusception was resected with end-to-end anastomosis. A colostomy was performed five days later because of a localized leak at the site of the anastomosis. The child died 12 days later of bronchopneumonia.

6 An eight-months-old child with a 12-day history of severe cardiac and respiratory difficulty, was transferred to this hospital in a moribund condition. He was placed in an oxygen tent and died 36 hours later. At autopsy, in addition to a severe cardiac anomaly, a gangrenous intussusception was found.

7 A five-year-old boy was admitted for the eighth time, with chronic lymphogenous leukemia, in critical condition. Hemorrhage from the spleen was suspected clinically but surgery was not considered. At postmortem, in addition to the leukemia, a gangrenous intussusception was revealed.

RESULTS

In 143 consecutive cases of infants and children whose signs and symptoms were sufficiently suggestive of acute intussusception to lead us to the final diagnosis, there were seven deaths, or a mortality of 4.8 per cent. One hundred and twenty-five of these cases were operated on and 18 were treated conservatively. In the operated group, there were five deaths, or a mortality of 4 per cent. In two patients, brought to the hospital in an almost moribund condition, the diagnosis was missed and death occurred. Two cases which were clinically felt to be intussusception were subjected to laparotomy and no intussusception was found. Both of these patients recovered.

There was one known recurrence in this series, the case was reoperated

There were 11 cases in this series, in addition to the deaths described above, in which complications occurred during the postoperative course. Of these, there were four cases of pneumonitis, all of which recovered. There were three cases in which a hernia occurred at the site of incision. Hematuria and anuria occurred in one patient, the etiology of which was undetermined. Otitis media occurred in one case, and an infection of the intravenous puncture wound occurred in two instances in which there was an otherwise uneventful postoperative recovery.

We feel that these good results have been obtained because of alert pediatricians whose early diagnosis has resulted in an average time interval of 28 hours between the onset of symptoms and surgery, and also because of the generally accepted practice of early operation as soon as a diagnosis of intussusception is made and the patient is prepared for operation, rather than prolonged conservative management.

We further feel that a division of cases into those with, and those without, severely damaged intussusceptum has greatly aided our staff in the proper management of preoperative, operative and postoperative care. This division seems to us of much more practical value than the division of cases on the basis of duration only, or by classification of the intussusception according to the location. Few preoperative measures are necessary in the group without any severe damage to the intussusceptum unless there has been considerable vomiting. Appendectomy can safely accompany the operation of reduction in this group. Little is needed in their postoperative care unless there has been an antecedent diarrhea. In contrast are those cases with severe damage to the intussusceptum which require preoperative transfusions and adequate fluid-replacement therapy, supportive measures during operation, a safe, rapid reduction of the intussusception, or resection if indicated, and no additional surgery, followed by extensive postoperative care. This must include blood and fluid, constant suction, antibiotics and chemotherapeutic agents and oxygen when necessary.

One death following an uncomplicated early reduction of a not severely damaged intussusceptum in an infant who had had a five-day period of severe diarrhea and a terminal severe gram-negative blood-stream infection, suggests to us that in similar future cases it may be wise to introduce one gram of streptomycin into the proximal small bowel through a fine-gauge needle at the time of surgery in addition to full parenteral administration of the antibiotics. This same procedure seems to us to be rationally indicated following the reduction of a severely damaged intussusceptum or after a resection.

SUMMARY AND CONCLUSIONS

1. During the last ten years the overall mortality rate of intussusception at the Children's Hospital has been 48 per cent. In 125 consecutive cases operated with reduction or resection, the mortality rate was 40 per cent.

2. We believe that these good results are due to (1) early diagnosis by an

alert pediatric staff, (2) general agreement that surgery is indicated as soon as the diagnosis has been made and the patient prepared, (3) proper preparation and aftercare with suction, fluid, electrolytes, blood and antibiotics

3 At operation, one gram of streptomycin in 3 cc of saline is injected, with a fine-gauge needle, into the bowel proximal to the intussusception in all cases with (1) a preceding history of diarrhea before the onset of symptoms of intussusception, and (2) whenever there is a severely damaged intussusceptum, regardless of whether or not this requires resection. We feel that this measure is an important supplement to the parenteral administration of antibiotics in avoiding local and generalized infections

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TOTAL PANCREATECTOMY FOR HYPERINSULINISM DUE TO ISLET-CELL ADENOMA

FOLLOW-UP REPORT FIVE AND ONE-HALF YEARS AFTER OPERATION,
INCLUDING METABOLIC STUDIES^{*}

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Although total pancreatectomy was performed by Minkowski¹ in the dog in 1889, obviously, this procedure could not be carried out with expectation of prolonged survival until after the discovery of insulin in 1921. Partial resection of the pancreas was performed in the human as early as 1882,² but only a relatively few cases of this type were reported until 1935 when Whipple's studies³ gave an impetus to this procedure. Since this time, partial pancreatectomy has been performed in numerous cases but, unfortunately, the late results of this operation, when used in the treatment of carcinoma, have not been wholly encouraging.

So far as we know, Rockey⁴ in 1943 reported on the first patient on whom total pancreatectomy was performed. The patient survived for 15 days after operation. Gaston⁵ in 1948 was able to collect data on 17 cases of total pancreatectomy from the literature.† Of the patients seven survived operation and ten died, an operative mortality rate of 59 per cent. Total pancreatectomy was carried out for neoplasm, tumors of the islets of Langerhans, and chronic pancreatitis with and without pancreatic lithiasis. More recently, careful observations on the metabolic changes which follow total pancreatectomy have been reported by Fallis and Szilagy.⁷ Obviously, with the limited experience that any one surgeon has had with this procedure, specific indications for its use are not yet well defined.

Apparently, the first patient who survived the immediate postoperative period after total pancreatectomy was reported by Priestley, Comfort and Radcliffe⁸ in 1944, 16 months after operation. This patient constitutes the basis for the present report as she has recently returned for a period of study, approximately five and one-half years after removal of the pancreas. The recent period of study affords opportunity for comparison of her present status with that observed during her early postoperative period in 1942. In the meantime, at the Mayo Clinic, three additional cases have been reported, and one additional total pancreatectomy has been performed for chronic pancreatitis with pancreatic lithiasis but has not yet been reported on.⁹

* Submitted for publication, March, 1949.

† One of the most completely studied of these cases was that reported by Ricketts, Brunschwig and Knowlton.⁶ The patient in this case was a white man, 52 years of age, who already had diabetes and chronic diarrhea. Pancreatectomy was performed for carcinoma. Subsequently, detailed metabolic studies were carried out.

After a brief review of the case history, the effects of total loss of the internal and external secretions of the pancreas as observed in the study of this patient in 1942 and again in 1948 will be discussed

REPORT OF CASE

A woman, age 49 years, registered at the Mayo Clinic July 6, 1942, because of symptoms which had been present three years. During this interval, she had experienced several types of attacks. The most severe episodes, of which there had been five during the previous three years, were characterized by loss of consciousness of from one to five hours' duration. These attacks required glucose administered intravenously for their relief. Minor episodes, which occurred more frequently, were characterized by sensations of dizziness or confusion, or spells of profuse perspiration. The latter spells occurred almost daily between 10 A M and 12 M and were promptly relieved by orange juice.

General physical examination showed the patient's weight to be 142 pounds (about 64.4 Kg) and revealed essentially normal findings. The systolic blood pressure was 140 mm of mercury and the diastolic, 80. All laboratory and roentgenologic studies also revealed normal findings except for those pertaining to the blood sugar. The fasting concentration of blood sugar was 42 mg per 100 cc. After a fast of 18 hours, the patient had a severe hypoglycemic reaction, starting with drowsiness and sweating and proceeding to loss of consciousness. The blood sugar at this time was 29 mg per 100 cc. The patient recovered from this spell after intravenous administration of 20 Gm of glucose, followed by oral administration of 200 cc of orange juice. A diagnosis of severe hypoglycemia, probably due to a hyperfunctioning tumor of the islets of Langerhans, was made.

Operation was performed on July 15, 1942. Exploration of the entire abdomen and the pancreas in particular failed to reveal any abnormality. At the suggestion of Dr R M Wilder, and because of previous unsatisfactory experience with partial resection of the pancreas under these circumstances, total pancreatectomy was performed*. A portion of the stomach was resected along with the duodenum and a posterior gastrojejunal anastomosis of the Polya type was established. Cholecystogastrostomy was performed and the common duct was ligated on the cephalic side of the pancreas.

The pathologist reported that the pancreas weighed 80 Gm. Only after a prolonged search was a cellular adenoma of the islets of Langerhans found. This was situated in the head of the pancreas, measured 8 by 5 by 5 mm, and was of the same consistency as the remainder of the pancreas and virtually of the same color.

The postoperative course was without particular event. The patient weighed 142 pounds (about 64.4 Kg) at the time of the operation, and 128½ pounds (about 58.3 Kg) at the time of dismissal on August 24, 1942, after a period of study in the metabolic unit.

The patient returned for re-examination on January 2, 1948, having remained in essentially good health in the interim. Her only complaints were of lack of energy and mild intermittent cramping abdominal distress. The latter symptom was relieved by moving the bowels. As a rule, she had three or four bowel movements each day, which were light in color and somewhat bulky. Her husband stated that, for the most part, her appetite had been ravenous. She apparently had a real craving for sweets, and her husband said she ate more sweets than the average person. She had taken no pancreatin because she had found that it caused abdominal distress. Neither had she taken any choline or other lipotropic substance other than that which was contained in her food. Although she did not diet systematically, so that there was considerable day-to-day variation in her food intake, it was estimated, on review of her dietary history, that her daily intake of choline had been in the neighborhood of 1,800 mg. Her weight had varied very little from the 128½ pounds (about 58.3 Kg) which she weighed at the time of her dismissal after the operation.

* It should not be thought that this procedure is routinely performed under such circumstances.

The interim history with respect to the behavior of the diabetes is given later in this paper under the heading "Effects of Total Loss of Internal Pancreatic Secretion"

The results of physical examination at the time of the patient's return in January, 1948, were essentially negative except for slight distention of the abdomen. Her weight was 124 pounds (about 56.2 Kg). The blood pressure was 130 mm of mercury systolic and 75 diastolic. Tendon reflexes of the lower extremities were all active. The arteries of the feet and legs were open. The results of examination of the ocular fundi and of routine urinalysis were normal. The value for hemoglobin and the erythrocyte count, leukocyte count and differential count were normal. Roentgenograms of the chest disclosed no abnormalities. Roentgenograms of the pelvis revealed evidence of vascular calcification. Roentgenoscopic examination of the gastro-intestinal tract revealed a normal pattern in the small intestine, and a normal colon and terminal portion of the ileum. Proctoscopic examination revealed a small polyp on the anterior wall of the rectum at 8 cm, which was fulgurated. The results of other laboratory studies are given subsequently.

EFFECTS OF TOTAL LOSS OF INTERNAL PANCREATIC SECRETION

After total pancreatectomy on July 15, 1942, the diabetic state was quickly established. Prior to removal of the pancreas, the fasting blood sugar had been as low as 29 mg per 100 cc; the morning after the operation, it was 341 mg per 100 cc. For the first three days after operation, the patient received solutions of glucose and sodium chloride intravenously, together with moderate doses of regular insulin, and glycosuria was fairly intense. Larger doses of insulin were employed in the immediate postoperative period than were subsequently necessary. The largest total dose for one day was 66 units. After the fifth postoperative day, it was possible to discontinue the intravenous administration of glucose and begin oral feedings. From this time forward, glycosuria was controlled with a single daily mixed dose of protamine zinc insulin and regular insulin, administered in the morning before breakfast. During the period of convalescence in the hospital, the total daily dose averaged approximately 30 units. The value of the fasting blood sugar varied over a wide range, from 60 to 340 mg per 100 cc but on most days it was less than 150 mg.

The course of the patient at home, with respect to the diabetes, in the interim between her dismissal on August 24, 1942, after pancreatectomy, and her return for a checkup on January 2, 1948, presented some interesting features. During the first three years at home she had taken each morning a mixture of protamine zinc insulin and regular insulin, totaling approximately 30 units, with fairly good control of glycosuria. For reasons which are not clear, she experienced almost continuous pruritus vulvae, which was apparently not related to the amount of glycosuria. In the latter part of 1945, on the suspicion that the pruritus might be related in some way to protamine, she changed to a mixture of regular and crystalline insulin, taken as a single dose in the morning before breakfast. The total daily dose varied from 28 to 40 units. No more insulin was taken during the remainder of the day. On this regimen she experienced an insulin reaction almost every afternoon, and almost every night after midnight she had symptoms of uncontrolled diabetes, that is

* It is of interest that roentgenograms of the lumbar segment of the spinal column in 1942 did not show evidence of vascular calcification.

thirst, polyuria and cramping of the legs. Intense glycosuria had been the rule on the first test in the morning. A few hours after the administration of the morning dose of insulin, the symptoms of uncontrolled diabetes would subside. The pruritus vulvae had been relieved.

The foregoing behavior of the patient's diabetes, while under treatment with a single morning injection of quick-acting insulin each day, suggests that it was of only moderate severity. In severe diabetes such as commonly occurs in children, adolescents and young adults, such a program of insulin administration is frequently followed by severe acidosis within 24 hours after the last dose of insulin, as a result of the waning action of insulin.

Further observation of the patient in the hospital between January 2 and January 16, 1948, provided additional evidence that her diabetes was of only moderate severity. During this period, she was treated with a mixture of protamine zinc insulin and regular insulin in a ratio of approximately one unit of protamine zinc insulin to two units of regular insulin, administered each morning before breakfast. The total daily dose varied from 18 to 24 units, depending on the results of fractional tests of the urine for sugar. The diet contained 269.6 Gm of carbohydrate, 117.5 Gm of protein and 101.6 Gm of fat. On this regimen, she excreted only small amounts of sugar in the urine, and experienced an occasional mild insulin reaction in the latter part of the afternoon. Ketone bodies were not found in the urine. On one day, when breakfast and lunch were omitted because of gastro-intestinal roentgenologic studies, the usual morning dose of insulin was withheld and no sugar appeared in the urine. This behavior again is in contrast to that commonly observed under comparable circumstances in persons who have severe diabetes.

EFFECTS OF TOTAL LOSS OF EXTERNAL PANCREATIC SECRETION

Digestion of Fat and Protein. This patient was studied in the metabolic unit for a period of 26 days during the early postoperative period in 1942, starting 12 days after operation. At this time, the diabetes was well controlled and she was taking a liberal diet of solid food. This study was divided into three periods with somewhat different relative caloric intake during each period. Details of this study have been reported previously.⁸ Suffice it to say at this time that the patient's diabetes was quite well controlled by proper administration of insulin. In contrast, digestion of protein and fat was definitely abnormal (Table I).

It was observed that approximately from 35 to 70 per cent of ingested fat could be accounted for in the stools. The average daily value for total fat lost was greater on the lower fat diet than on the high fat diet. Fat composed from 37 to 54 per cent of the fecal solids. Administration of pancreatin in gelatin capsules did not significantly affect the absorption and digestion of fat. Studies of ingested nitrogen revealed that from 25 to 55 per cent was present in the stools. The daily loss of nitrogen varied from 2.92 to 8.28 Gm. Computing the fecal nitrogen in terms of protein, average daily fecal protein accounted for from 25 to 39 per cent of the fecal solids. Fat and protein accounted for from

73 to 79 per cent of the fecal solids. Nitrogen balance was positive at all times, despite the large losses in the feces.

During the period of metabolic study in January, 1948, the patient was given a standard test diet¹⁰ consisting of 117.5 Gm protein, 18.8 Gm nitrogen, 101.6 Gm fat and 269.6 Gm carbohydrate, which furnished a total of 2,463 calories. No pancreatin or lipotropic substance was given during this period. Studies of the fecal content entirely similar to those made during the early postoperative period were repeated. Values of the fecal content of normal persons ingesting this diet and of the patient under consideration are shown in Table I. It is apparent from this table that the several values are greater

TABLE I—Average Daily Values for Fecal Total Solids, Fat and Nitrogen in a Case of Total Pancreatectomy and in Normal Persons

		Fat				Nitrogen		Dietary Intake	
Date and Period No	Total Solids*	Total*	Per Cent	Per Cent	Total*	Per Cent	Fat*	Pro- tein*	Carbo- hydrate*
			Total Solids	Ingested Fat		Ingested Nitrogen			
Total Pancreatectomy									
1942	Period I†	131 97	48 19	37	70	8 28	55	69 0	241
	Period II	83 94	36 28	43	35	4 07	38	102 5	206
	Period III†	73 4	39 8	54	42	2 92	25	95 0	222
1948	Period IV	108 0	52 2	48	51	8 20	43 5	101 6	269 6
Normals									
Mean§	27 6±2 2	4 1±0 5	14 5±1 1	4 0±0 5	1 7±0 1	8 9±0 8	101 6	117 5	269 6
Standard deviation	7 3	1 5	3 7	1 7	0 4	2 6			

* Grams

† The durations of Periods I, II, III and IV were, respectively, 10, 10, 5 and 3 days.

‡ During Period III, the patient received daily 28 Gm of powdered pancreatin (Parke-Davis) in gelatin capsules.

§ The figure after the ± is the standard error of the mean.

than the upper limits of normal. Those for total fat and percentage of ingested fat as fecal fat are more abnormal than those for total fecal solids, fecal solids which are fat, total fecal nitrogen and percentage of ingested nitrogen as fecal nitrogen. Nitrogen balance was positive during this short period of study.

Fecal values obtained during the period of study in July and August, 1942, immediately after operation, cannot be compared with exactness with those obtained in January, 1948, because of differences in dietary intake, but it appears that the interim of five and one-half years between these two studies has not altered the disturbance of digestion and absorption found during the period immediately after pancreatectomy.

Blood Lipids and Hepatic Function. The values for plasma lipids were not determined before pancreatectomy but the concentration of bilirubin was 1.2 mg per 100 cc (indirect) and the sulfobromophthalein-sodium test of hepatic function did not disclose retention of dye. During the period immediately after operation, the concentration of plasma cholesterol, cholesterol esters, lecithin, fatty acids and total lipids were, respectively, 216, 121, 301, 397 and 613 mg per 100 cc, values which are within the normal range.

Five and one-half years later, in January, 1948, the respective values for cholesterol, cholesterol esters, lecithin, fatty acids and total lipids were 210, 120, 392, 596 and 806 mg per 100 cc. The concentration of bilirubin in the serum was 0.7 mg per 100 cc (indirect). The sulfobromophthalein-sodium test of hepatic function did not disclose retention of dye. The concentrations of total serum protein, albumin and globulin were respectively 6.5, 4.7 and 1.8 Gm per 100 cc, alkaline phosphatase was 2.6 units (Bodansky) and the cephalin-cholesterol flocculation and thymol turbidity reactions were negative.

Neither total pancreatectomy nor huge losses of fat in the feces had appreciably altered the concentration of plasma lipids or the functions of the liver, which were measured.

Such effects are dissimilar to those occurring in pancreatectomized dogs. When a pancreatectomized dog is maintained with insulin and a diet adequate to maintain a normal dog, infiltration of the liver with fat decreases the requirement for insulin and decreases the output of sugar in the urine and about a 50 per cent reduction in blood fats develops. These changes may take place within four or five weeks or earlier and are well developed by the twentieth week after pancreatectomy.^{1, 2, 4, 7, 13} The reduced function of the liver is measurable by the sulfobromophthalein-sodium test. A lipotropic substance, either raw pancreas, lipocaic, lecithin or choline,^{11, 14, 18} must be added to the diet to prevent these changes. Dragstedt, Clark and Vermeulen¹¹ found that the minimal effective daily dose of choline for a dog weighing from 9 to 12 Kg is about 1 Gm.

In the case reported here, the patient has received a mixed diet for more than five years. The diet is estimated to contain approximately 1,800 mg of choline per day. She has not taken pancreatin, lipocaic, raw pancreas or supplementary choline or methionine. On this program, the hypolipemia or disturbed hepatic function found in the pancreatectomized dog has not developed. A similar failure of hypolipemia and fatty liver to develop in the case of total pancreatectomy for carcinoma, when examined eight months later, has been reported by Dixon, Comfort, Lichtman and Benson.¹²

The authors are indebted to Miss Gordon Sampson, chief dietitian, Mayo Clinic metabolic unit, St. Marys Hospital, for her careful planning and supervision of the diets used in this study.

SUMMARY

The clinical course and results of metabolic studies in a patient who had undergone total one-stage pancreatectomy five and one-half years previously for hyperinsulinism due to a small adenoma of the islets of Langerhans are reported. Similar studies on this patient were reported in 1944 by Priestley, Comfort and Radcliffe⁸ 16 months after the operation. During the five and one-half years after pancreatectomy the patient remained in essentially good health. Her diabetes continued to be of relatively mild degree as compared with the type of diabetes which commonly occurs in children, adolescents and young adults. In spite of the loss of large amounts of nitrogen and fat in

the feces, she was able to maintain an excellent nutritional state. The values for blood lipids and serum proteins remained within the normal range, and there was no abnormality of the functions of the liver which were measured, in spite of the fact that her diet had not been supplemented with choline, lecithin or other lipotropic substance.

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VARICOSE VEINS*

FURTHER FINDINGS BASED ON ANATOMIC AND SURGICAL DISSECTIONS

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THE THERAPY of varicose veins was improved greatly by the introduction of high ligation of the long saphenous vein¹ Nevertheless, it has become evident to students of the subject that this procedure alone or in association with retrograde or other forms of injection often fails to produce maximum benefits Many workers, including this author, believed that the failure of this form of therapy was due to incompetent thigh perforator veins² Studies that were undertaken to establish the role of these veins in the etiology of varices were the subject of an earlier report³ They involved anatomic dissections on 73 cadavers (137 thighs) and 465 patients (703 limbs) This work clarified the anatomy of the saphenous vein on the medial aspect of the thigh and knee and also established a method of locating perforator veins in the area This knowledge was then applied to the operative care of varicosis The surgical dissections confirmed the anatomic pattern but surprisingly demonstrated that thigh perforators are not as frequently incompetent as was previously believed This knowledge made it imperative to search elsewhere for the solution of the problem

The investigations were then directed to the study of the perforator veins distal to the knee In the course of this work, dissections were carried out on 63 cadavers (92 legs) and observations were made on 482 patients involving 901 lower extremities It was found that incompetent leg perforators are very numerous and much more often responsible for incomplete therapy than are the thigh perforator veins

It is the purpose of this paper to present the results of these anatomic and surgical studies and to describe additional operative technics that have been devised to deal with the new findings

ANATOMIC STUDIES

The distribution of perforator veins connecting the two saphenous systems with the deep veins in the leg varies somewhat, but if adjustments are made for differences in height, a remarkable constancy in their placement is observed, similar to that in the thigh The anatomic placement of perforators in the lower extremity may be divided into five main groups first, those on the medial aspect of the lower extremity, second and third, the lateral aspects of leg and foot, fourth, the short saphenous system, and fifth, muscular perforators in the calf

The first of these divisions deals with the medial aspect of the entire lower extremity Figure 1 shows the venous pattern on the medial aspect of the

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VARICOSE VEINS

thigh, in a somewhat more simplified form than was previously reported³ Figure 2 illustrates the scheme of veins on the medial aspect of the leg. In the thigh the main long saphenous vein B' (Fig 1) is situated beneath the superficial layer of the deep fascia. This deep fascial layer is continued uninterrupted down the leg to the base of the toes, as a distinct enveloping

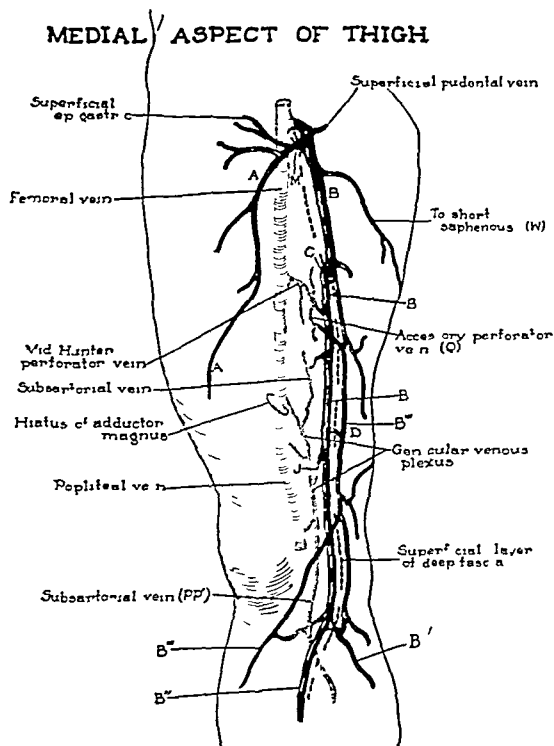


FIG 1—Drawing showing the saphenous as A, A', and B, B', B'', B'''. Veins A, A', B lie superficial to the deep fascia, whereas distal to C, veins B', B'' lie beneath the superficial layer of the deep fascia. B''' emerges from beneath the deep fascia at D.

The constant mid-Hunter canal perforator vein connects the main saphenous vein B' with the femoral vein.

The genicular venous plexus connects the femoral and popliteal veins with the subsartorial vein. The subsartorial vein makes connections with the main long saphenous vein B' in the thigh and continues distally in the leg to make connections with B', B'', and posterior tibial vein.

Accessory perforator vein Q emerges into the superficial fascia without making direct connections with the main saphenous stem B', B''. Perforator vein J makes direct connection between main saphenous stem B'' and the subsartorial vein.

Line M illustrates the danger of mistaking superficial vein A for the main long saphenous vein in patients who possess double long saphenous veins.

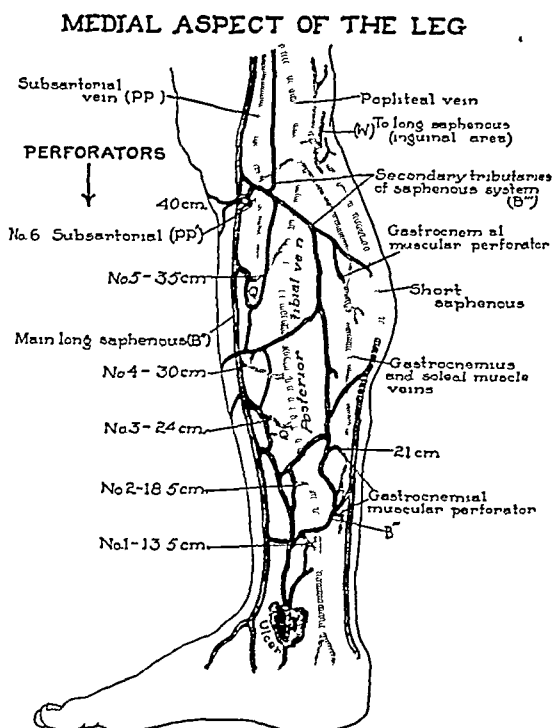


FIG 2—Drawing showing the saphenous systems as B', B'', and short saphenous vein. The secondary saphenous tributaries B''' are black and indicate their placement within the superficial fascia. The lightest tinted crosshatching indicates veins situated beneath the traditional deep fascia. The medium tinted crosshatching (vein B' and lower part of short saphenous vein) depicts veins lying between the extension of the deep fascia of the thigh and the traditional deep fascia.

Perforator veins 3, 4 and 5 connect the posterior tibial vein with the main long saphenous vein B'. Perforator veins 1 and 2 connect the posterior tibial vein with secondary saphenous veins B''. Perforator No. 6 connects the posterior tibial and subsartorial veins with veins B' and B'''.

Accessory perforator vein Q emerges into the superficial fascia without making direct connections with vein B'.

All measurements start from the sole of the foot.

sheath, separate from and overlying the traditional deep (crural) fascia of the leg. The primary main long saphenous vein B'' continues down the leg between this extension of the deep fascia of the thigh and the traditional deep fascia of the leg. Vein B'' lies adjacent to the medial border of the tibia, makes connections with the deep veins of the leg by perforators and communicates with the more superficial veins (B''') by vessels that pierce the extended superficial fascial layer of the deep fascia of the thigh.

An analysis of Figure 2 shows that perforator veins 3, 4, 5 and 6, located in the upper part of the leg, make direct connections between the main long saphenous vein (B'') and the posterior tibial vein. On the other hand, perforator veins 1 and 2, located in the lower part of the leg, rarely make direct connections between these main veins. Instead, they connect with secondary veins (described as vein B''') which in turn join with the main long saphenous vein (B''). These secondary saphenous veins (B''') are significant because they are the origin of most of the leg perforators. A closer study of the perforator veins on the medial side of the leg demonstrates that within restricted limits their placements and patterns are quite constant.

Perforator No 1 (Fig 2) is situated about 13.5 cm above the sole of the foot and about 2 cm posterior to the medial border of the tibia. Perforator No 2 is located about 18.5 cm above the sole of the foot and about 1 cm medial to the medial border of the tibia. Rarely do either of these perforators make direct connections with the main long saphenous vein (B''). Instead, nearly always they make connections between superficial secondary tributaries (B''') and the posterior tibial vein. Incidentally, these perforators often join a superficial secondary tributary (B''') that connects the main long saphenous vein (B'') and the short saphenous vein.

Perforators Nos 3, 4 and 5 (Fig 2) are adjacent to the medial border of the tibia. They are situated about 24 cm, 30 cm and 35 cm above the sole of the foot, respectively. They usually make direct connections between the long saphenous vein (B'') and the posterior tibial veins, and their locations are quite constant. Occasionally one of these perforators is absent, in which case its function is compensated for by an adjacent perforator. These perforators also usually possess accessory perforator (Q) veins or collaterals, which make independent junctions with secondary veins (B''').

Perforator No 6 is located about 40 cm above the sole of the foot and 1 cm medial to the medial border of the tibia. It makes connections between the main long saphenous vein (B'') and superficial veins (B'''), on the one hand, and the subsartorial vein (PP') and the posterior tibial vein, on the other hand. As described in a previous article³ and also indicated in Figure 1, PP' is a continuation of the genicular plexus. Proximally it communicates with the highest, superior and inferior genicular veins, and distally courses deeply beneath the traditional (crural) deep fasciae, to make the connections with the veins above described. During anatomic dissections it has been observed that this vein (PP') may continue distally, even as far as perforator No 2,

and has been seen to make connections with any of the perforators from 2 to 6 inclusive

Perforators on the medial aspect of the foot and ankle also exhibit much constancy. The anterior medial malleolar perforator is located about 5 cm above the ankle joint. It arises from the main long saphenous vein (B'') adjacent secondary veins (B'''), and deep veins of the foot. From the anterior medial aspect of the foot it courses behind the tendons of the tibialis anterior and extensor hallucis longus to join with the anterior tibial vein.

There are three perforator veins about 4 cm above the sole of the foot on the medial side. They are located about 9 cm, 8 cm and 5 cm anterior to the posterior border of the heel, respectively. They make connections between superficial veins (B'''), vein B'', on the one hand, and the deep veins of the foot, on the other.

A group of three or more perforators is located about 3-5 cm anterior to the posterior border of the tendo achillis, and they range from 5 cm to 10 cm above the sole of the foot. A fairly constant perforator is located near the upper edge of the internal malleolus about 5 cm anterior to the posterior border of the tendo achillis. These four or more perforators connect secondary tributaries B''' and the medial tributary of the short saphenous vein, on the one hand, and the posterior tibial vein and deep veins of the foot, on the other. No drawings were made of the perforator veins on the medial aspect of the foot and ankle, as their clinical significance seems relatively unimportant.

The second general division concerns those perforator veins on the lateral aspect of the leg which usually lie in the intermuscular septum between the peroneal longus and brevis muscles, on the one hand, and the gastrocnemius and soleus muscles, on the other (Fig. 3). They make connections between the superficial secondary veins (B''') and the peroneal vein. In the proximal part of the leg these superficial veins usually connect indirectly with the posterior tibial, anterior tibial or popliteal veins. These perforators also usually make connections with the veins draining the gastrocnemius and soleal muscles. Often, instead of lying in the intermuscular septum, they pierce the lateral border of these muscles to connect with the peroneal vein as well as with the muscular veins. In addition, the peroneal perforators make connections with the veins draining the peroneal muscles. Although considerable variation in their longitudinal placement is observed, and some perforators may be absent, in general they are found at about 5 cm intervals between points 10 cm and 45 cm above the sole of the foot.

The third group of perforators, also located on the lateral side of the leg, lies in the intermuscular septum between the peroneal longus and the brevis muscles posteriorly, and the tibialis anticus and extensor longus digitorum muscles anteriorly. They connect the superficial secondary tributaries (B''') with the anterior tibial vein at about 16, 22, 29, 31-35 and 39 cm, respectively, above the sole of the foot.

In general, the perforator veins on the lateral aspect of the foot and ankle unite the short saphenous and secondary veins (B''') with the deep veins of

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the foot At a varying level from 5 to 10 cm above the sole of the foot and just anterior to the tendo achillis there is a group of three or more perforators These may also course deep or superficial to the tendo achillis to anastomose with the posterior tibial vein Numerous other perforators are found in this region They may be identified by measuring their relationship respectively to the posterior line of the heel and to the sole of the foot The placement of these perforators is 3.5 to 4.5, 4 to 6.5, 4 to 5, 6 to 3, 8 to 3, 7.5 to 4 and 10 to 3 cm, respectively

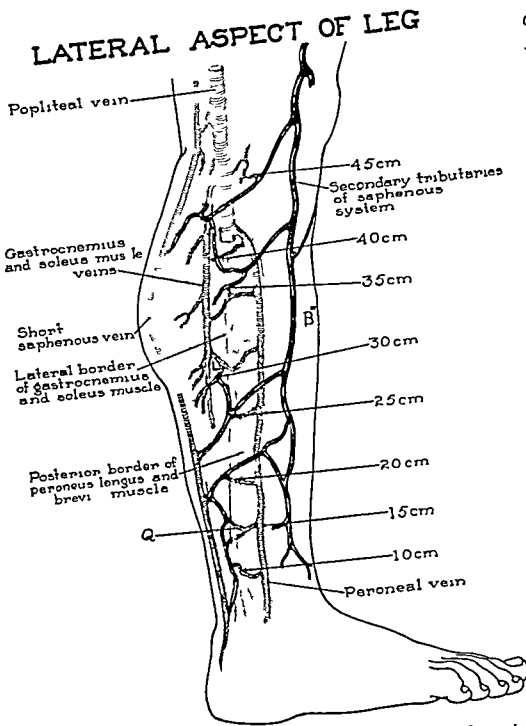


FIG 3—Drawing showing perforator veins situated in the intermuscular septum between the gastrocnemius and soleus muscles, on the one hand, and peroneal muscles, on the other The perforator veins connect the peroneal vein with secondary saphenous tributaries B''' A perforator vein (L) is depicted as emerging through the lateral border of the gastrocnemius or soleus muscles Connections between the perforator and muscular veins are indicated Accessory perforator vein Q emerges to connect with secondary saphenous tributary B''' at a different site than a companion perforator vein All measurements start from the sole of the foot

POSTERIOR LEG PERFORATORS

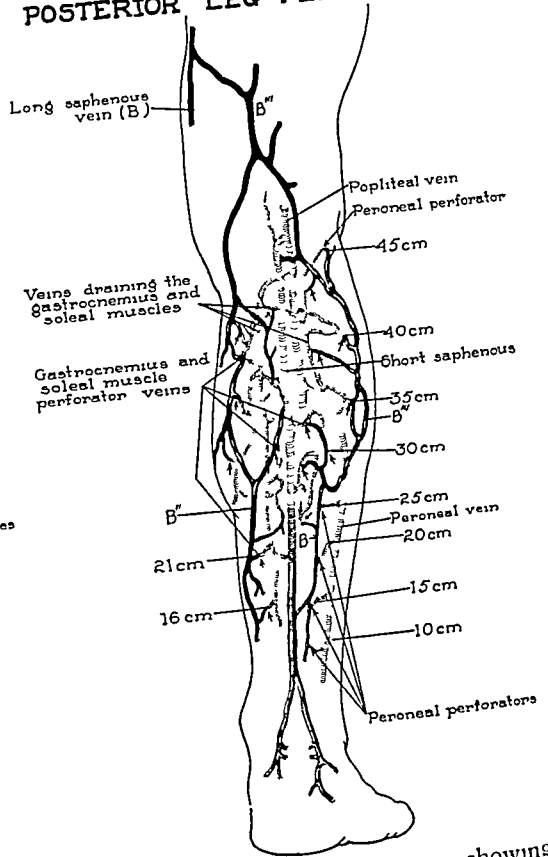


FIG 4—Composite drawing showing sites of perforator veins on the posterior aspect of the leg Perforators connect the short saphenous vein and secondary saphenous tributaries B''' with muscular veins draining the gastrocnemius and soleus muscles In general, there are four longitudinal lines of perforators Two of these are within 2 cm of either side of the midline, and the other lines are three or more centimeters lateral or medial to the midline There are usually four or more perforators in each of the three medial lines and only one or two in the lateral longitudinal line In the latter group the absence of perforators is compensated for by drainage through the peroneal perforator veins

Arrows indicate site of perforators Note perforators indicated at 16 and 21 cm They might be confused with perforator No 1 or 2, as shown in Figure 2 All measurements start at the sole of the foot.

The fourth group is located posteriorly and mainly concerns the short saphenous vein. The upper part of the latter vein is situated beneath the traditional (circular) deep fascia of the leg, whereas in the lower part of the leg and foot it lies more superficially between the traditional deep fascia and the extension of the superficial layer of the deep fascia of the thigh, in which respect it is similar to the main long saphenous vein (B'') in its placement between fascial layers. The short saphenous usually makes a single or double connection with the popliteal vein in the hollow of the knee, but variations are numerous. Of these variations, several are outstanding and occur more often than is generally believed. The short saphenous may have no connection with the popliteal vein, or the connection may be a very small one. Instead, it may unite with deep thigh veins, especially with those veins draining either the lateral or the medial (hamstring) muscles. Again, the short saphenous vein may continue proximally up the thigh to make its connection at various levels with the inferior gluteal or profundis femoris vessels. An outstanding divergence is a short saphenous vein that again makes only trivial, if any, connection with veins in the popliteal area. Instead, this vein W (Figs 1 and 2) courses proximally up the posterior and the medial aspect of the thigh to join with the saphenous vein about 5 cm distal to the saphenofemoral junction. Other perforators near the midline posteriorly make direct connections with the short saphenous vein and indirect connections with the veins draining the gastrocnemius and soleal muscles (Fig 4).

The last group of perforators (Fig 4) comprises the veins that make connection between the superficial veins (B''') and the short saphenous vein, on the one hand, and the muscular veins of the gastrocnemius and soleal muscles, on the other. Only a few of these veins make direct union with the short saphenous, most of them connect with the very superficial secondary B''' tributaries of both the long and the short saphenous systems. They enter deeply, and within the muscles communicate with other muscular veins, terminating in larger veins which join the posterior tibial vein about a centimeter distal to the traditional saphenopopliteal junction. As a generalization, there are four longitudinal lines of perforators, two are within two centimeters of either side of the midline and the other two lines are three or more centimeters lateral or medial to the midline. The most proximal of these is 45 cm, and the most distal one is 10 cm above the sole of the foot. There are about four perforators in each of the three medial lines and only one or two in the lateral longitudinal line. In the latter group the absence of perforator veins is compensated for by drainage through the peroneal perforator veins.

Three principal findings resulted from these anatomic dissections. (1) The main long saphenous vein (B''), in the leg and foot, courses distally adjacent to the medial border of the tibia and is situated deep to a distinct fascial layer that is continuous with the deep fascia of the thigh. (2) The lower part of the short saphenous vein, although superficial to the traditional deep fascia of the leg, is also deep to the fascia which is a continuation of the deep fascia of the

leg (3) The perforator veins of the leg and foot are numerous, and, in general, fit into a rather easily established pattern

SURGICAL APPLICATION

The successful treatment of incompetent perforator veins depends upon a full understanding of the patterns described, and especially of the characteristics of the saphenous tributaries B, B', B'', B''', the mid-Hunter canal perforator system, the genicular plexus and the anatomic distribution of perforator veins in the leg. The significance of this understanding is illustrated by the observation that although the elimination of the deep, long saphenous stem B' and B'' disconnects the direct communication of the saphenous vein with the femoral or popliteal veins, it does not destroy the indirect connection through the accessory perforator veins (Q, Fig 1). In like manner, in the leg, eradication of the main long saphenous vein (B'') disconnects direct communication of the saphenous vein (B'') with the posterior tibial vein but does not eliminate the accessory perforator veins (Q, Fig 2).

The surgical procedure based upon the information gained from the anatomic studies described has, in our hands, improved the results of the therapy of varicose veins. It consists of a combination of injection of veins, high ligation, elimination of the main saphenous stem (B', B''), eradication of the mid-Hunter canal perforator vein, elimination of incompetent perforators connected with the genicular venous plexus and excision of all incompetent perforators in the leg or foot. The judicious use of a sclerosing solution⁴ as an agent for the suppression of hemorrhage, especially in the lesser saphenous tributaries, is very helpful in controlling bleeding at the time of operation.

PROCEDURE

The patient is examined for evidence of systemic disease, peripheral arterial disorder and postthrombophlebitic sequelae. The presence of edema, eczema, indurated areas or ulcerations is noted. Much importance is laid on inspection and palpation of the limbs. Large venous bulbs and especially defects in the fascia are sought, as these abnormalities often have been found to be the site of incompetent perforator vessels. Their locations are recorded and, prior to operation, are identified by skin markings with a weak silver nitrate solution.

Minor varicose veins may be sclerosed by local injection previous to operation. Under spinal analgesia or general anesthesia the saphenofemoral junction is exposed and a standard high ligation is performed. In order to control bleeding more effectively, a retrograde injection of about 3 cubic centimeters of a sclerosing solution may be injected into the saphenous vein. In the majority of patients with double long saphenous veins, most of the tributaries at the upper end of the saphenous system arise from vein A (Fig 1). A ligation performed as indicated by M (Fig 1) would leave the main long saph-

enous vein B patent, and the operative procedure would fail to accomplish its purpose

The next step is the elimination of the saphenous and perforator veins in the thigh. Although incompetent perforator veins in the thigh are not common, nevertheless occasionally huge perforators exist and the vein B'', which lies under the superficial layer of the deep fascia, must be diligently explored for possible incompetent perforators. If any are found they must be eliminated. A description of this procedure was detailed in a previous article.³

The next step consists of elimination of varices and incompetent perforator veins in the leg (Fig. 2). An incision about 4 cm. long is made on the inner aspect of the leg, just below the knee. This is made obliquely, with the lateral end about 2 centimeters distal to the medial end. Thus the veins B'' and B''', which were previously removed from the thigh, are exposed. From either or both of these veins superficial tributaries often course anteriorly or posteriorly. If they are varicose they are excised. In particular, the secondary tributary (B''') that courses posteriorly often connects with the short saphenous vein in the mid-calf area, and along its route incompetent perforators may be found. They pierce the deep fascia and extend deep in the gastrocnemius muscle. When present, they are dissected within the gastrocnemius muscle, where they are ligated and transected.

The main long saphenous vein (B') is grasped and examined for possible incompetent perforator veins 5 and 6, which are located about 35 cm. and 40 cm. above the sole of the foot, approximately in the middle of the upper third of the leg. Vein B' is then followed distally, stripping the vein digitally and at the same time feeling for large perforator veins. Very small competent perforators are broken off with the fingers, but over any incompetent perforators a longitudinal incision is made and the perforator eradicated deeply. Next, a longitudinal incision, 3 cm. in length, is made about 25 cm. above the sole of the foot at the medial border of the tibia (Fig. 2). This incision allows B' to be picked up and perforators 3 and 4 examined. As there is a possibility of perforators not connecting directly with vein B', judicious use of the dissecting fingers and retractors will aid in locating pathologic perforators. This incision may be extended distally or proximally, as necessary.

For perforator No. 2, a longitudinal incision is made about 19 cm. above the sole of the foot and 1 cm. medial to the medial border of the tibia, and this area is searched for secondary tributaries. Such veins are meticulously followed until one or more are found that course deeply, the deeper tributary very likely being the perforator. Also very helpful is the use of digital dissection. The subcutaneous tissue is stripped away from the deep fascia and either a weakness in the fascia can be felt or the perforator is located by hooking the index finger around it as it emerges through the deep fascia.

Superficial secondary veins (B''') in this area can be followed distally and posteriorly and may connect with perforator No. 1 or with medially located calf perforators.

Perforator veins located at a greater distance than 15 cm medial to the medial border of the tibia, in this area, are usually gastrocnemius or soleal muscular perforator veins

If perforator No 1 is suspected of being incompetent, a longitudinal incision is made about 14 cm above the sole of the foot, 2 cm medial to the medial border of the tibia (Fig 2) Superficial secondary veins (B'') are sought, especially the one that often makes connection between vein B' and the short saphenous (Fig 2) With meticulous dissection deeply penetrating veins are sought After eliminating this perforator, vein B' is stripped to a point about level with the ankle, where it is ligated and transected

Attention is then given to perforators on the lateral aspect of the leg A longitudinal incision is made over previously marked sites and carried down to the deep fascia by blunt dissection The area is explored with the index finger, and the subcutaneous tissue is stripped away from the deep fascia, so that the finger is hooked about the offending perforator, which is then dissected for at least 2 cm below the deep fascia, where it is ligated and transected

The next step is elimination of the rarely involved perforators at the medial or lateral aspect of the ankle or foot They are treated in like manner

The patient is turned over and the marked sites on the calf are explored The perforator in this area must be followed deep within the muscle before ligating and transecting If the short saphenous vein is involved, it is ligated and transected at its junction with the popliteal vein, or if perchance no such connection appears to exist, at least the ligation is made adjacent to the popliteal artery All tributaries of the short saphenous must be ligated and transected Occasionally, as a variation, a large short saphenous vein makes only a trivial connection with deep veins within the popliteal space It may course, first proximally on the posterior aspect of the thigh, and then medially to connect with the long saphenous vein 4 to 6 cm distal to the saphenofemoral junction W (Figs 1 and 2) If such a condition exists, it may be excised if desired, but the retrograde flow of blood is, of course, eliminated by the high ligation at the saphenofemoral junction

Although not common, incompetent perforators on the lateral or posterior aspect of the thigh occasionally exist If present, they should be ligated at a point deep beneath the fascia and if possible at their junction with a major vessel of the deep venous system

In order to emphasize the meticulous care that must be exercised in order to efface reflux of blood through incompetent perforator veins, Figures 5 to 8, inclusive, are presented The method of treating perforators on the medial aspect of the leg (perforators 1 to 6 inclusive) is illustrated by perforator pattern (Fig 5) Two perforators are depicted as emerging through the same fascial opening If the ligation should be performed at the indicated incorrect site, the reflux of blood would route itself through the accessory (Q) perforator In order to secure success, the ligation must be made very deep beneath the fascia, at the point noted as the "correct site for ligation of per-

forator" Figure 6 is similar to Figure 5 except that the possibility of the accessory (Q) perforator emerging from a different opening in the fascia is shown. The behavior of the perforators on the lateral aspect of the leg is indicated in Figure 7. The placement of the perforator is shown to be mainly in the intermuscular septum between the soleus and the gastrocnemius muscles, on the one hand, and the peroneus longus and brevis, on the other hand. The correct site for ligation is shown to be very deep in order to eliminate reflux of blood through either the main perforator or the accessory perforator (Q) vein. This drawing also illustrates the connection of the peroneal perforators

PERFORATOR PATTERN

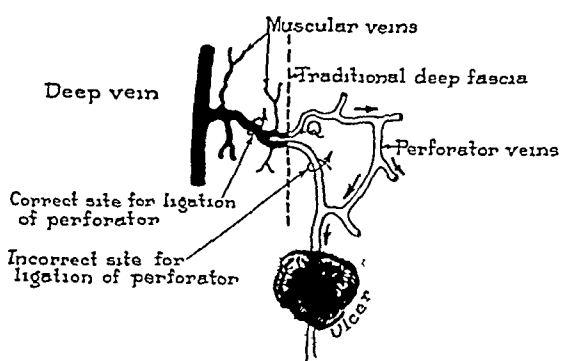


FIG 5—Drawing illustrating method of treating incompetent perforator veins on medial aspect of the leg. Two perforators are shown as emerging through a single fascial opening. If ligation were performed at the indicated incorrect site, the reflux of blood would route itself through the accessory perforator Q vein, as indicated by the arrows. The ligation must be made very deep beneath the fascia at the point noted as the "correct site for ligation of the perforator"

PERFORATOR PATTERN

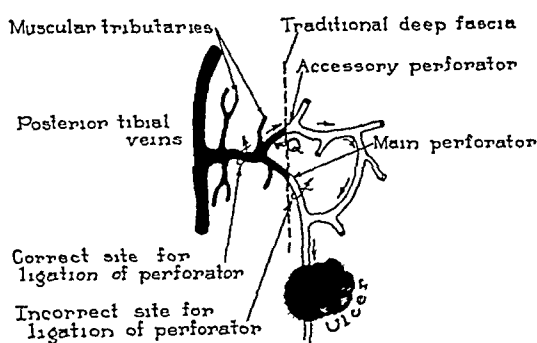


FIG 6—Drawing illustrating method of treating incompetent perforator on the medial aspect of the leg. This figure is similar to Figure 5, except that the possibility of the accessory Q perforator vein emerging from a different opening in the fascia is shown. If the ligation were not performed at the indicated correct site, the reflux of blood would route itself through the accessory perforator Q vein, as indicated by the arrows

with the veins draining the gastrocnemial and soleal veins. In fact, the main peroneal (P) vein may be absent, its function being supplanted by the Q vein near the lateral border of the gastrocnemius or soleus muscles. Hence, in such exceptions, although the perforator (Q) vein must be followed through the muscle, nevertheless the correct site for ligation is the same as depicted in the drawing. In this case the connection between the Q and gastrocnemius vein (G) must also be severed. Figure 8 concerns the treatment of perforators in the calf of the leg. Again it is to be observed that, in order to eliminate reflux of blood through incompetent perforators, the dissection must be made deep within the muscle.

The futility of the so-called stripping procedure or eversion of the long saphenous vein by the Babcock probe method is illustrated by comparing Figure 9 with Figure 2. These drawings are identical except that in Figure 9 the main long saphenous vein (B'') has been removed. Although some direct connections between the main long saphenous vein (B'') and the deep veins

have been interrupted, the collateral and accessory perforator (Q) veins have been left intact and the procedure has failed to accomplish its purpose

The operative time for one extremity is approximately three hours. Usually both lower extremities are treated simultaneously, in which case the presence of at least one additional competent surgeon is advisable. Teamwork is very helpful.

Following operation, the patient is wrapped from the groin to the ankle in roller gauze, and adhesive bandages are snugly applied in order to prevent swelling. Because of the multiplicity of incisions, the patient is given 300,000 units of duracillin every 12 hours from the time of admission until discharge.

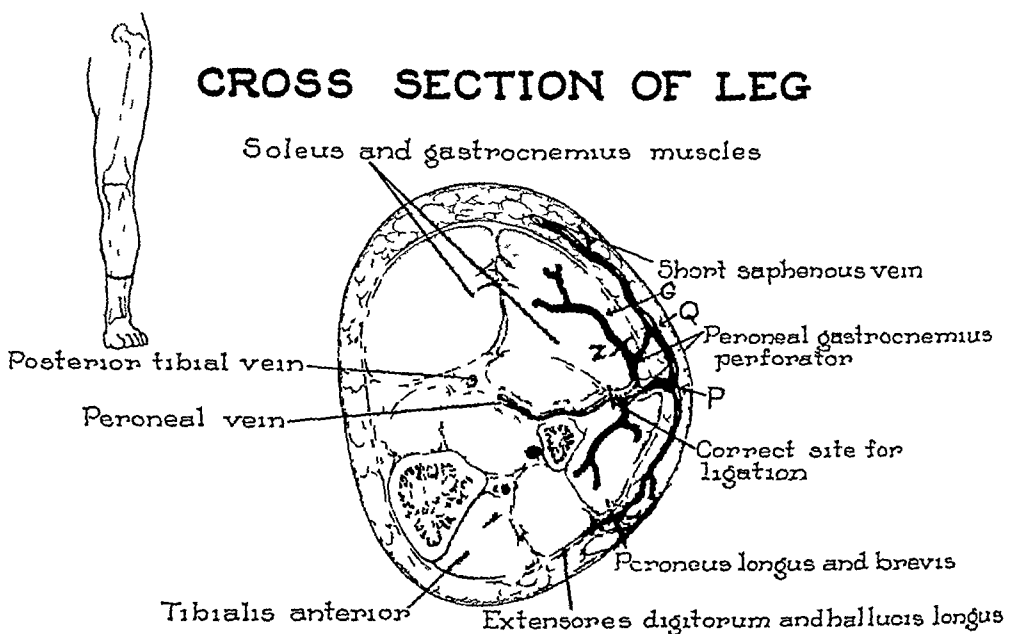


FIG 7—Drawing illustrating a method of treating incompetent perforators on the lateral aspect of the leg. The perforator is shown to be in the intermuscular septum between the gastrocnemius and soleus muscles, on the one hand, and the peroneus longus and brevis, on the other. In order to prevent the reflux flow of blood through either the perforator P vein or the accessory perforator Q vein, the ligation must be made very deep at the point noted as the "correct site for ligation." The connections between the main perforator vein, the accessory perforator Q vein, and the G veins draining the gastrocnemius and soleus are indicated. The muscular G vein must also be ligated at point Z.

When sufficiently recovered from anesthesia, patients are instructed to move their legs vigorously in bed and are encouraged to walk. The following morning all patients are thoroughly ambulated and are personally conducted up and down stairs. They leave the hospital the same day with verbal and printed instructions. They are particularly instructed to walk at least 5 out of every 30 minutes during the day. Any type of activity is encouraged. The sitting position is not allowed for four weeks, except for short intervals to partake of meals. When tired, they lie down. They are also informed that a temperature up to 102 degrees Fahrenheit is not unexpected.

VARICOSE VEINS

DISCUSSION

Recent surgical experience since 1944 has confirmed the belief that a new method of thinking is essential to adequate correction of varicosities. The present commonly accepted procedure of high ligation with or without retrograde injection, although of considerable benefit in some patients, leaves very much to be desired. It is believed that to obtain ideal results a much more radical surgical approach is necessary.

I do not agree with the opinion that incomplete filling of veins in 30 or more seconds as observed in the Trendelenburg "positive" tests indicates the

LONGITUDINAL SECTION OF CALF

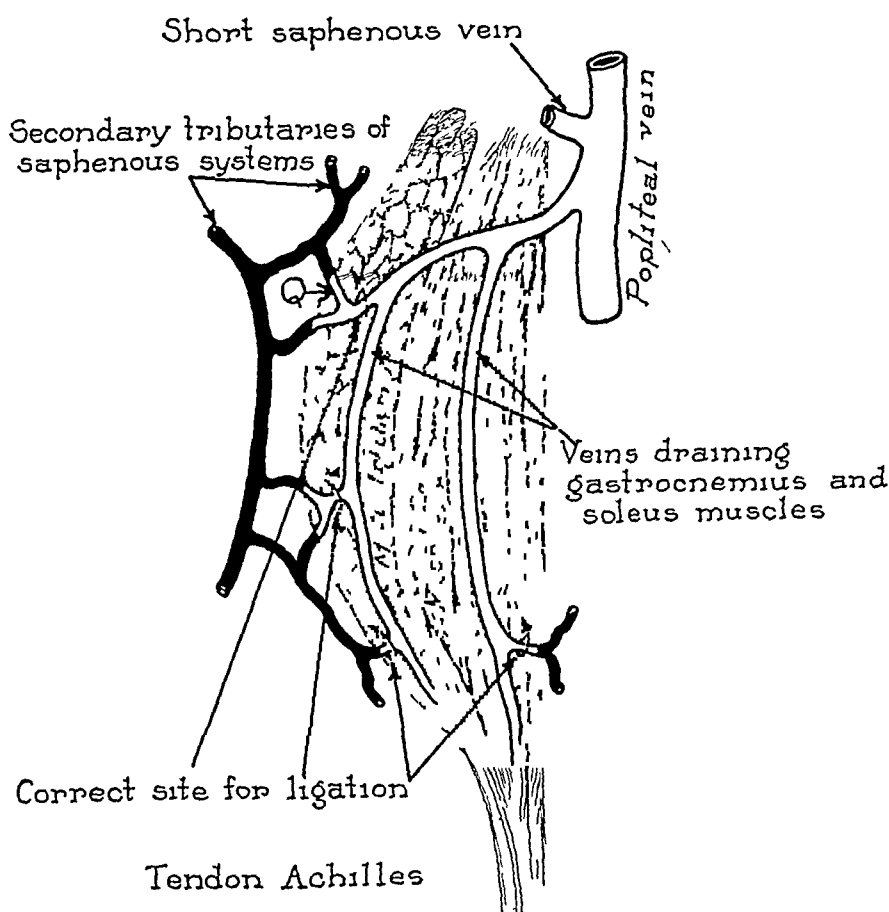


FIG 8—Drawing illustrating method of treating incompetent perforator veins in the calf. In order to prevent reflux of blood through the accessory Q vein, the ligation must be deep within the muscle at the point designated as "correct site for ligation."

absence of incompetent perforator veins in the leg or thigh.⁷ Indeed, about 95 per cent of the surgically treated cases were Trendelenburg "positive" and in 823 out of 901 lower extremities obvious pathologic perforator veins were found (Table I).

The failure of high ligation entirely to prevent recurrences of varicose veins was correctly believed to be due to incompetent perforators below the saphenofemoral junction. During multiple tourniquet tests the fact that the

filling of veins occurred much less rapidly when the tourniquet was placed below the knee than when placed at the groin resulted in the assumption that most of the deficiency was due to incompetencies in the thigh. The failure of the multiple tourniquet tests to locate the incompetent thigh perforators² led

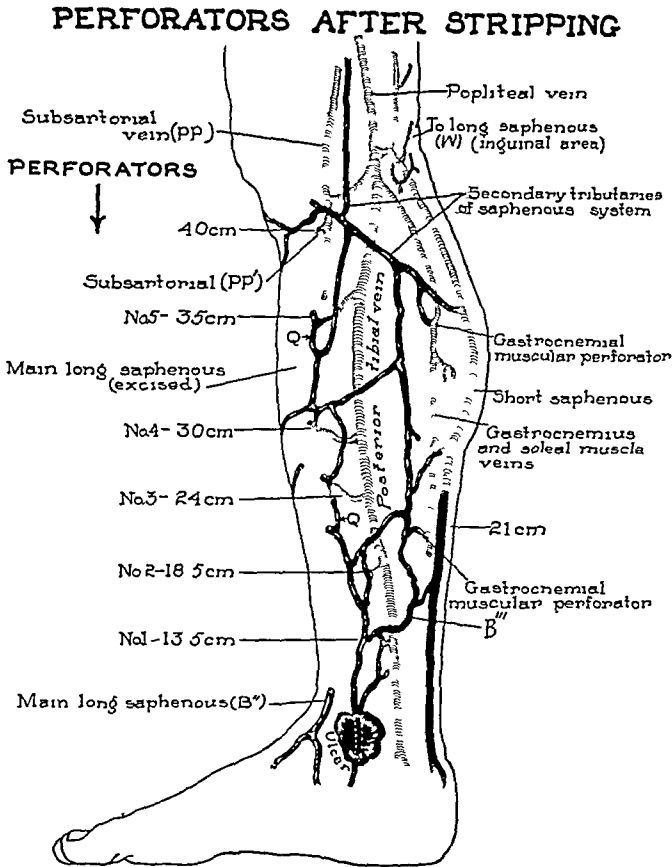


FIG 9—Drawing illustrating the futility of the so-called stripping procedure. This figure is identical with Figure 2, except that the main long saphenous vein B' is pictured as being excised. The direct connections between the deep veins and the main long saphenous vein B' are interrupted, nevertheless the collateral and accessory perforator Q veins are undisturbed. The reflux of blood through the incompetent leg perforators is not altered and the procedure fails to accomplish its purpose.

All measurements start from the sole of the foot.

to further anatomic and surgical studies. These explorations revealed that incompetencies in the thigh are relatively rare (about 9 per cent) and therefore could not be responsible for the inadequate results so frequently observed (Table II). Similar studies on the leg, however, showed incompetent perforator veins to be very common and often of huge size. These latter findings adequately explain the frustration experienced by many of us when attempting to locate incompetent perforators in the thigh. They seldom existed.

The number of incompetent perforators in a single extremity varies. The largest number found was 14, the smallest, one. The numerical and percentage

distribution of incompetent perforators is detailed in Table II. The most common offender is perforator No. 2 (34.8 per cent). The high incidence of incompetent short saphenous vein (15.2 per cent), perforator No. 3 (19.8 per cent) and perforator No. 1 (16.6 per cent) should be noted. On the lateral

TABLE I—*Distribution of Incompetencies in Operated Cases*

Number of patients	482
Number of lower limbs	901
Number of right lower limbs	452
Number of left lower limbs	449
Number of lower limbs with perforators	823
Number of lower limbs without perforators	78

aspect of the leg, as shown in Table II, most incompetent perforators are found in or near the intermuscular septum between the gastrocnemius and the soleus muscles, on the one hand, and the peroneal muscle group, on the other. The perforators most often responsible for the nonhealing of ulcers in order of importance are perforators Nos. 2, 3, 1 and the short saphenous vein.

It is very important to realize that there is no known key vein governing vulval varicosities. The incompetent perforator or perforators responsible for this reflux flow of blood cannot be eradicated and consequently it is

TABLE II—*Distribution of Incompetent Perforator Vessels on 901 Lower Limbs*

	Number Right	Per Cent	Number Left	Per Cent
Saphenofemoral junction	452	100	449	100
Saphenopopliteal junction	67	15	70	15.5
Mid-Hunter canal perforator	31	7	29	6.7
Genicular perforators	13	2.9	9	1.6
Lateral thigh perforators	8	1.8	6	1.3
Perforator No. 1	72	15.9	77	17.3
Perforator No. 2	155	34.3	158	35.2
Perforator No. 3	90	20	85	19.6
Perforator No. 4	59	13	57	12.7
Perforator No. 5	30	6.6	31	7
Perforator No. 6 (PP')	19	4.2	14	3.1
Perforators in calf	54	12	50	11.2
Perforators between gastrocnemius and peroneal muscles	113	25	108	24
Perforators between tibialis anticus and peroneal muscles	14	3.1	12	2.9
Perforators lateral border of tibia	1	.02	2	.04
Lateral foot perforators	9	2	11	2.4
Medial foot perforators	16	3.5	12	2.9

obviously unwise to operate on women in the child-bearing age.⁶ The operation does no harm, but subsequent pregnancies dramatically demonstrate the futility of the procedure. After the menopause, in order to alleviate the varicose condition, the suggested operation may be performed, with the realization that the results are not entirely satisfactory.

Although 1,367 radical surgical dissections have been made, adequate knowledge of perforator veins in the leg has only been attained since the latter part of 1944. Accordingly, the surgical results are based only on these recent cases (Table III). The failure to achieve perfect results can, in most

cases, be traced to one or more incompetent perforators, usually small, that were overlooked during the operation. In the entire group of varicose-vein patients no deaths or massive hematomas have occurred. There were 23 mild infections and 3 rather severe infections. Seven mild embolisms occurred. Six of these had, as the only symptom or physical finding, a slight lancinating pain in the chest of two or three days' duration. The seventh patient, who had slightly bloody sputum, was without symptoms after two weeks. The average time of hospitalization was 214 days. All patients were walking

TABLE III—*Study of Cases 3, 2 and 1 Years, Respectively, After Operation**

	Right Limb			Left Limb		
	1 Year	2 Years	3 Years	1 Year	2 Years	3 Years
Number of cases	157	98	58	154	96	56
Average per cent improvement	98.6	97.8	97.6	98.1	97.5	97.3
* 19 cases possessing vulval varicosities and 9 cases of preoperative thrombo phlebitic sequelae not classified						

within 28 hours after operation. The average time of returning to work was 15 days. Ace bandages are worn until all edema subsides (about six weeks).

As a result of these studies I have become convinced that the efficacy of any treatment of varicose veins is in direct proportion to the ability of the operator to eradicate incompetent perforator veins wherever they are located.

SUMMARY

1. A general scheme of arrangement of the saphenous systems in the leg exists, and locations of perforator veins are fairly constant.

2. The occurrence of a heretofore unrecognized location of the main saphenous vein and lower portion of the short saphenous vein between deep fascial layers is described.

3. Incompetent perforator veins are relatively rare in the thigh.

4. Incompetent perforator veins are very common in the leg, and one of the usual interpretations of the Trendelenburg "positive" test is challenged.

5. Suggestions are made for what appears to be a more effective operative therapy.

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CHRONIC STENOSING REGIONAL ENTERITIS SURGICAL PATHOLOGY AND EXPERI- ENCE IN SURGICAL TREATMENT*

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In 1934, two years after the original description of regional ileitis by Crohn, Ginzburg and Oppenheimer,¹ our first opportunity to operate on such a case arose. In the following 14 years, we have operated on 30 patients with regional enteritis or ileocolitis. In conjunction with the Department of Gastroenterology of the Graduate Hospital, we have carefully followed the progress of these patients. With the passage of time, we have had a splendid opportunity to appraise the results of the therapy of the earlier cases. The immediate results were very encouraging. However, with longer and more adequate follow-up, it became evident that the good results were not always permanent. We were forced to reoperate upon many of these patients because of recurrences or progression of the disease. Others manifested clinical or roentgenographic recurrences, but were maintained by intensive medical regimens. These recurrences took place, in spite of the fact that we employed a very radical operative approach and performed resection of the diseased bowel whenever possible.

Since the description of the disease by Crohn *et al*,¹ and the histologic description by Hadfield,² very little has been added to our understanding of the etiology or pathogenesis of regional enteritis. A review of the pathology as we have seen it might therefore be of interest. From our observations of the gross and microscopic pathology, we believe that regional enteritis, ileocolitis, and regional colitis are manifestations of the same disease in different segments of the intestine. This does not include ulcerative colitis which first involves the sigmoid or rectum in 95 per cent of the patients³ and is a different entity clinically and pathologically.

In our series, we have seen five types of the condition classified as to location. They are regional duodenitis, jejuno-ileitis, terminal ileitis, ileocolitis and regional colitis. In four patients, the lesions have been confined to the jejunum or ileum (not terminal). Eight patients had involvement of the terminal ileum. Fifteen cases were examples of ileocolitis. In two patients, the site of involvement was limited to a segment of the colon, and in these there was no disease in the sigmoid-rectum characteristic of distal ulcerative colitis. In one case, the duodenum was involved in a process which grossly resembled chronic stenosing regional enteritis.⁴ To our knowledge, a lesion of this nature in this area has not been reported previously.

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We have recognized three phases of this condition the acute, the chronic and the chronic with complications

The mimicry of acute appendicitis by regional enteritis is well known We have operated upon patients for acute appendicitis and found the appendix normal, but the ileocecal area involved in the acute phase of regional enteritis In one, the serosa of the distal ileum was markedly hyperemic, its texture was fine granular, the subserosal tissues were edematous, and the glands in the adjacent mesentery were enlarged and hyperemic Appendectomy did not relieve this patient of her symptoms, and roentgenographic survey a month later confirmed the presence of ileocolitis

The abdomen in the acute phase usually contains a small amount of free fluid This may be serosanguineous, clear, or turbid, depending upon the presence of exudate The site of involvement may be any of the four previously described The serosal vessels are injected and the bowel is fiery red and the serosa is covered with a thin fibroplastic exudate The diseased loops "stick" together with thin friable, fibrinous adhesions and the wall of the bowel is definitely edematous The mesentery of the involved segment is hyperemic and moderately edematous, and its surface seems to "weep" fluid The mesenteric glands are enlarged and congested, though the degree of enlargement varies, and some may attain a diameter of 2 cm The color of the glands ranges from pale pink to deep red or a violaceous hue In some instances, these enlarged glands are confined to the mesentery of the diseased segment of intestine, in others, they may be widely scattered throughout the entire mesentery from its base to its bowel attachment We have not observed the acute phlegmonous type with perforation as described by Homb⁵

Histologic descriptions of the acute phase have been few because resection of diseased bowel is not attempted at this time Homb⁵ describes the picture as an infiltration of all layers by inflammatory cells lymphocytes, leucocytes (many of them eosinophilic), large mononuclear and plasma cells This is characterized by an enormous edematous thickening of the submucous coat and dilatation of the vessels is noted The mucosa in this stage may be intact, or shallow ulcerations filled with mucopurulent debris may be present, though usually small

In one patient, we made a preoperative diagnosis of subsiding acute appendicitis and found, at laparotomy, an acute ileocolitis which appeared to be subsiding The lesion was resected contrary to our usual practice When the bowel was opened, three large ulcers were found, just proximal to the ileocecal valve, the smallest of these measuring 1 cm in diameter and the largest 2 cm The edges were not overhanging, the bases were shallow and filled with mucopurulent exudate, and the mucosa between was hyperemic and markedly edematous No evidence of involvement of the subserosal lymphatics was present

When the chronic phase of this disease is reached, the gross picture changes The involved bowel is thickened and stiff, and it has been adequately described as "hose-like" The serosal surface may be covered with a fibro-

plastic exudate as seen in the acute phase, but often this has become organized into thick fibrous tissue which is contracted and stenoses the bowel. A striking feature is the overgrowth of the mesenteric fat on the serosal surface, which tends to encircle the diseased segment of small bowel, and frequently none of the antimesenteric border is visible in the area of greatest involvement. We have not observed this in the colon. The bowel proximal to the stenotic area may appear to be entirely normal, or, if some obstruction exists, it will be dilated. The change can be an abrupt one. Usually this proximal bowel is hyperemic for a few inches orad and has some sticky exudate on its serosal surface.

Palpation of the involved area in a classic case reveals a "rubbery" or "boggy" feel, with marked thickening, and the lumen seems absent. This can be compared to the normal, soft, velvety feel of the bowel above. In Crohn's original description, this was most marked in the ileum adjacent to the ileocecal valve, however, we have observed marked involvement in other portions of the jejunum-ileum or colon. We have seen as many as five different areas of involvement in a single patient, each separated from the other by normal ileum. The occurrence of these so-called "skip areas" is well recognized.

The mesentery of the diseased bowel is usually thick, edematous, and rubbery. The mesenteric vessels are not visible, and in cases with extreme thickening, the pulsations may not be palpable. The nodes are almost always enlarged as in the acute phase, and they are discrete, soft and fleshy.

When the bowel is opened, the mucosa appears hemorrhagic, the villi edematous and bulbous, and this hypertrophy gives a "cobblestone" appearance to the mucosa. The hypertrophy may be so marked that the mucosa is polypoid. Varying amounts of mucosal ulceration and destruction are present and the ulcers are often shallow, discrete and contain a dirty grey necrotic exudate. These ulcers tend to occur on the mesenteric side of the lumen, but we have seen them at any location on the wall. In the areas of greatest ulceration, the induration and cicatrization of the bowel wall are most marked. There may be regions of attempted healing of the mucosal defects, and here the mucosa is atrophic, flat and glistening.

The thickening of the bowel is tremendous and gives rise to a marked narrowing of the lumen. Grossly, all coats are thickened but the submucosa shows the greatest increase. As one passes up the bowel, there is a progressive enlargement of the lumen and decrease in breadth of the wall. The limits of the overgrowth of the antimesenteric fat often coincide with a termination of the mucosal ulceration and bowel thickening.

The chronic stage may be complicated by the presence of obstruction, peritonitis, abscess formation and fistulas. Obstruction has its origin in contraction of the stenotic areas, and dilatation and edema of the proximal bowel is noted. Peritonitis of the spreading type from a free perforation has not occurred in our series, the extreme thickening of the submucosa probably forms a strong barrier against rapid perforation of an ulcer. Perforations usually occur late in the course of the disease and are walled off to form a

localized abscess Burrowing into the mesentery is common This abscess, together with the involved ileum and mesentery, forms a rather firm inflammatory mass which may be in the pelvis or along the vessels in the iliac fossa These abscesses may perforate into adjacent bowel loops that are matted together and result in internal fistulas, and these may invade any of the hollow visci, in one case, an ileosigmoid fistula was present These fistulas may burrow externally through the abdominal wall

The appraisal of the extent of colonic involvement in ileocolitis has not been easy in many of our patients At times, the terminal ileum and cecum show distinct evidence of advanced disease, but there is no abrupt termination of the process in the colon when external examination is made There may be a slight suggestion of congestion and edema of the wall of the colon with no involvement of the mesentery, yet when this colon is opened, its mucosal surface may abound with small ulcerations This was met with in one of our recent cases

The colon that is extensively involved will show the same thickening and contraction of the wall as is seen in the small intestine, and fibroplastic or fibrostenotic exudate may appear on its serosal surface In our experience, the mesentery is not as thick and edematous, it often is firm and shortened due to fibrosis The presence of visibly affected glands varies, and in several of our patients with advanced colonic disease, only minimal lymph gland involvement was noted In one case of ileocolitis, the right half of the colon was much more destroyed than was the terminal ileal segment, yet the lymph glands in the mesentery of the small intestine manifested the greatest enlargement and inflammation

The complete classical picture of the gross pathology is not present in every case It should be stressed that many variations occur and are a source of confusion in the determination of the limits of the disease Perhaps this contributes to the high rate of recurrence following resection because the lesion is not always completely eradicated For example, some cases do not show marked thickening and narrowing of the bowel, but have a soft, flabby wall with no diminution in the size of the lumen, and serosal exudate may be entirely lacking One may see great thickening of the mesentery with little or no overgrowth of fat on the serosal surface of the bowel Lymphadenopathy may range from minimal to widespread Furthermore, the picture in the chronic stage may be complicated by a superimposed acute exacerbation of the process

The microscopic appearance of the bowel wall in chronic stenosing regional enteritis has been most adequately described by Hadfield² He has stressed the thickness of the submucosal coat as being directly proportionate to the thickness of the bowel wall, and has stated that hypertrophy of the muscular coat is inconstant and variable in degree and is usually prominent only in the late stages of the disease The submucosal lesion is characterized by hyperplasia of the lymphatic tissue and an obstructive lymphedema, the former being

non-specific in type. He emphasized the replacement of the germinal centers making up a nodule of lymphadenoid tissue by a marked proliferation of the reticulo-endothelial cells. In the middle of these cell systems, Langhans' type of giant cells are often seen. These clear-cut giant-cell systems resemble military tuberculosis without caseation. The same picture is noted in the available lymph glands. As mucosal ulceration progresses, secondary inflammation occurs, and the giant-cell systems may be obscured by a secondary lymphadenitis characterized by diffuse inflammation and fibrosis.

In some of our cases, the mucosal lesion has been striking. Aside from the superficial ulcerations with diffuse cellular exudate and secondary inflammation of the crypts, other changes of the mucosa are noted. Mucosal hypertrophy is often a prominent feature and this is particularly marked in the villi, where hyperemia and new blood vessel formation may be seen. Regions of interstitial hemorrhage may be evident, and fibroplastic activity is present in the mucosal layer, which may be in degree enough to amount to frank scar formation.

This histologic picture has not been limited to the small intestine and its mesentery in our cases of ileocolitis. We have identified the same lesion in the colon and its mesentery. The hyperplasia of the lymphoid tissue is not as marked as in the terminal ileum because of the progressive decrease in the amount of lymphoid tissue in the submucous coat of the colon from the cecum caudad.

In considering the surgical treatment of this disease, it is necessary to define the stage of the pathological process—that is, the acute or the chronic phase with or without complications. A remission of the acute stage can often be obtained by rigorous medical management if an abscess or obstruction has not developed. Even when these complications arise, there is occasionally a subsidence of the acute phase while the patient is being prepared for operation. A regression of the acute stage is not always followed by stenosis or other sequelae. Some do not progress to obstruction, abscess formation or fistulization. It is in this category that we believe rigorous medical management, as outlined by Bockus,⁶ may have as much in its favor as surgical intervention. No operation should be attempted in a patient known to be in the acute stage of this condition without complications.

In the cases that simulate acute appendicitis, exploration is advisable to rule out a pathological process in the appendix. If the appendix is found to be normal, and an uncomplicated acute ileocolitis exists, it is best to terminate the procedure. Many believe that removal of the appendix under these circumstances is often followed by fistulas because the disease is actually present in the cecal wall and is not recognized. Because of the likelihood of remission and the lack of preparation of the patient, we do not advocate resection of the lesion during this stage. In fact, three of the 17 cases reported by Pugh⁷ were of this type and all subsided after laparotomy without definitive surgery. If the picture is complicated by an abscess, drainage is necessary.

In the surgical management of the chronic stage, two types of operation are employed. One consists of resection of diseased bowel and primary anastomosis. The other procedure is a transection of the ileum above the site of the lesion and anastomosis of the normal ileum to the colon distal to the lesion. The ileal stump just above the lesion can be closed or it can be brought out through a stab wound as a mucous fistula to act as a safety-valve if the terminal ileum is partially obstructed.

TABLE I—*Results of Radical Resection*

Total number of resections	24
Operative deaths	2
Cases followed less than 1 year	7
	—
	9
Cases closely followed from 1-14 years	15
Number of proved recurrences	11
	—
Recurrence rate	73%

In our earlier experience with this disease, we assumed that wide excision of the involved ileum or colon would result in a cure. A long segment of terminal ileum approximately two feet above the level of the disease and the proximal half or two-thirds of the colon were usually resected. In two patients, all of the ileum and right half of the colon were removed. The mesentery was excised as close as possible to its base. It was often impossible to remove every vestige of thickened mesentery and involved lymph glands without endangering the blood supply to the remaining bowel. We thought that removal of the diseased bowel would allow the process in the remaining mesentery to subside. An early favorable response to this type of operation caused us to continue with the method of attack, however, later follow-up observations revealed that recurrences took place after the most radical resections.

TABLE II—*Time Elapse Between Resection and Recurrence*

	Number of Cases
1-2 years	5
2-3 years	3
3-5 years	1
5-10 years	2
	—
Total	11

Resection of the diseased bowel was performed in 24 of the patients with two deaths—an operative mortality of 8.3 per cent. Five of the resections have been followed for less than a year and should be excluded from the series when results are considered. This is important because all but one of our recurrences took place after one year had elapsed. One patient died of malnutrition one month after operation, and another patient was committed to an asylum and lost for follow-up purposes. There remain 15 patients who

have been carefully followed from one to 14 years. Eleven recurrences, based on clinical and roentgenographic examination, have taken place in those 15 cases—a recurrence rate of 73 per cent (Tables I and II).

These discouraging results have caused us to modify our views, and in the past two years we have elected to use ileocolostomy with exclusion of the diseased bowel in six cases. The results of Garlock⁸ and Colp⁹ with this type of operation have been exceptionally good, and the surgical mortality from this operation is very low.

The cases of chronic stenosing regional enteritis which are classified as complicated are best treated by the short-circuiting and exclusion operation. The case with a large abscess walled off by adjacent loops of diseased bowel and complicated by an infiltrative process in the mesentery cannot be resected safely. Large obstructing inflammatory masses can also be treated by a side-tracking operation with less hazard. Similarly, when the diseased bowel is densely adherent to the posterior parietes or to the vessels along the lateral pelvic wall, it is unwise to attempt a resection. Internal and external fistulas are further indications for ileocolostomy with exclusion.

The six cases in which we performed this type of operation were all complicated ones. Two had had radical resections before but had developed recurrences. In addition, a gastro-jejunostomy was performed on the patient with duodenal involvement. Four of these remain symptom free after a two year follow-up. In one case, a transection of the terminal ileum and ileotransverse colostomy with exclusion was performed. One year later there was a definite recurrence in the ileum proximal to the anastomosis. She was reoperated upon and the ileum was transected above the site of the recurrence and anastomosed to the distal transverse colon. The distal stump of transected ileum was brought out as a mucous fistula. The inflammatory mass present in the right iliac fossa at the first operation had entirely disappeared. All gross evidence of disease in the excluded ileum had disappeared. This section of bowel was found to be soft and collapsed and the serosa was pale and shiny. No enlarged glands were present in the mesentery. The entire colon appeared normal. Six months after the second operation, her disease again became active, and roentgenographic study revealed a second recurrence at the anastomotic site. She was again explored, and the colon distal to the anastomosis was markedly involved. This is of interest because the process had previously been confined to the small bowel, but recurrence took place in the colon. An ileostomy was necessary to divert the fecal stream from the diseased bowel. She died three months later of inanition.

The presence of widespread mesenteric lymph gland involvement is an indication for the exclusion operation. Cases with extensive involvement of the small intestine or multiple "skip areas" should be treated conservatively. One of our cases was operated on by a surgeon well trained in the recognition of this process. Four skip areas were present in the ileum, therefore, he closed the abdomen without any surgical attack on the lesions. She was treated

medically for three years and finally died following our attempt to relieve a multiple obstruction. We believe that his keen judgment allowed this patient three years of uncomplicated survival.

Occasionally a case with involvement of the colon from the ileo-cecal area to the sigmoid is seen. In such a case, we elect to do an ileostomy well above the site of the disease in the ileum. If the lesion becomes quiescent and does not progress into the distal sigmoid, restoration of bowel continuity by ileosigmoidostomy may be attempted. It is wise to observe these cases for a period of two to three years before restoring the continuity of the bowel. One case had an extensive enteritis in the terminal ileum complicated by an obstructing mass adherent to the sigmoid colon. The sigmoid was involved by contiguity. An ileostomy was made above the lesion. He improved markedly, and three years later, he insisted that the ileostomy be taken down. At the second operation, the distal sigmoid was found to be partially obstructed by scar tissue. Therefore, the terminal ileum was anastomosed to the ascending colon, and a colostomy proximal to the sigmoidal obstruction was performed. We reasoned that a left-sided colostomy would be easier for the patient to care for than a high ileostomy, and the colon from the cecum to the sigmoid had been free of involvement. At the second laparotomy, it was noted that the excluded ileal segment which had been badly diseased, appeared normal. The mass along the sigmoid and the fistulous tracts had all disappeared. The only evidence of old inflammation was the contracted scar on the distal sigmoid colon. When the abdomen was opened at the second operation, the ileum proximal to the ileostomy appeared normal. However, after the slight trauma of inspection and palpation, the serosal surface became edematous and hemorrhagic. Therefore, a segment 35 cm. in length above the ileostomy was excised and the remaining ileum was anastomosed to the ascending colon. When this resected segment of ileum was opened, small mucosal ulcerations were noted and microscopy revealed the typical tubercle-like nodules in the lymphoid tissue of the submucosa. We believe that this man will have a recurrence at the anastomotic site.

SUMMARY

- 1 The surgical pathology of chronic stenosing regional enteritis as we have observed it has been reviewed.

- 2 In our early experience with this disease, we performed radical resection of the diseased bowel with the hope that a cure would result. In the ensuing years, recurrences took place in such a large percentage of the cases, that we are convinced that resection is no longer the procedure of choice.

- 3 The less radical procedure advocated by Garlock has accomplished as much, and even though we have had recurrences from this type of operation, it is attended with much less morbidity and mortality.

- 4 It is difficult to understand our large percentage of failures following resection when the results are compared with those from other clinics practicing resection. Our cases have all been carefully followed by the Depart-

ments of Surgery, Gastroenterology and Radiology Under such close scrutiny, some who were clinically well were eventually found to present some evidence of recurrence We can only assume that longer and more intensive follow-up surveys in series from other clinics will reveal a higher recurrence rate

5 As a result of our experience with this condition, we believe that surgical intervention should be confined to those cases complicated by obstruction, abscess, fistulas, and those in which a most thorough medical regimen has failed

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FURTHER EXPERIENCES WITH STREPTOMYCIN THERAPY IN PERITONITIS*

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THIS STUDY of streptomycin in the treatment of fecal peritonitis is a continuation of a preliminary report¹ published in December, 1947. The 85 cases upon which it is based include 54 of the cases analyzed in the earlier report. All data, as in the first report, are derived from case histories submitted to the Office of The Surgeon General as part of a special study of streptomycin in various Army installations.

Certain of the points made and certain of the literature cited in the introductory remarks to the first report might properly be repeated here. (1) Peritonitis resulting from perforation of hollow viscera is a polybacterial infection caused by a variety of aerobic and anaerobic bacteria, chiefly *Escherichia coli*, aerobic and anaerobic nonhemolytic streptococci, and *Clostridia*. (2) The reduction recently evident in the mortality rate of peritonitis represents the summation effect of chemotherapy (antibiotic therapy), intestinal decompression, and the correction of fluid and electrolyte imbalance and of protein depletion, not the effect of chemotherapy or antibiotic therapy alone.

Experimental and clinical studies by various observers permit certain conclusions as to streptomycin therapy. According to Silvani,² streptomycin has no demonstrable prophylactic or therapeutic value in canine peritonitis and sodium sulfadiazine in large dosages is equally ineffective, though penicillin in large dosages affords considerable protection. The beneficial effect of penicillin therapy seems to lie in the eradication of gram-positive bacteria, when this has been accomplished, gram-negative bacteria, which are relatively non-invasive, disappear spontaneously.

Lockwood³ defines peritonitis as a local disease which produces a profound systemic reaction and, in effect, causes death by shock. The methods of treatment which have been conspicuously effective all increase the patient's tolerance to the shock-producing factors in the disease. The most important of these measures are deliberate, careful preoperative preparation, correction of perverted metabolic, electrolyte and water balance, the use of blood, plasma and oxygen, gastrointestinal decompression, and the administration of chemotherapeutic and antibiotic agents. Obviously, as Lockwood points out it is exceedingly difficult to evaluate in any mathematical way the relative significance of any one of these therapeutic measures, including the use of

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chemotherapeutic and antibiotic agents. In his opinion the important role of the latter agents can be explained by their ability to modify the severity of the toxic reaction of the host to bacteria and bacterial products in the peritoneum. One of these effects, their ability to interrupt bacterial synergism, is of outstanding significance in fecal peritonitis, even though the drugs may not be active against all the flora present in a given case, their ability to restrain the activity of gram-positive cocci seems to modify the tendency of the disease to spread. A second important factor is the ability of the sulfonamides and penicillin to limit the production of bacterial toxins and thus minimize that amount which the patient must absorb.

ANALYSIS OF DATA

The 85 cases of peritonitis reported in this communication represent a collection begun in January, 1946. They form a heterogeneous group in

TABLE I—*Result of Streptomycin Therapy in Fecal Peritonitis*

Therapy	Type of Peritonitis	Good	Negative
Streptomycin alone	Spreading	8	1
	Local	4	5
	Total	12	6
	% of Total	67%	33%
Streptomycin and penicillin	Spreading	31	8
	Local	20	8
	Total	51	16
	% of Total	76%	24%

respect to age, etiology, scheme of dosage and duration of therapy. All received comparable management. Many of the more desperately ill patients were given combined therapy at the beginning of treatment to provide for maximum coverage. While the age range was from 2 to 62 years, 66 patients were between 17 and 30 years of age and only 14 were over 45 years of age.

The origin of the infecting organisms is best classified according to the level of the gastrointestinal tract affected. In the majority of cases involving the large bowel (59) the infection originated in the appendix. In the small bowel the pathogenesis was variously volvulus of the jejunum, entrance into the small bowel, as the result of trauma, duodenal ulcer, Meckel's diverticulum, and an infection following pancreaticoduodenectomy. Gastric lesions resulted from perforation of peptic ulcers and traumatic perforation of the stomach.

The type of peritonitis for the sake of simplicity, was classified as *spreading*, in which the process was early or was so massive that the normal forces of localization were not apparent, and *local*, in which localizing forces were evident.

Results (Table I) are grouped into two categories, one indicating definite benefit from the therapy given (Good), and the other indicating questionable or no benefit (Negative). Criteria of a good result include (1) the establishment of a downward trend in the temperature curve within 48 hours of the institution of the drug or drugs, and the absence of any subsequent rise

FIG 1

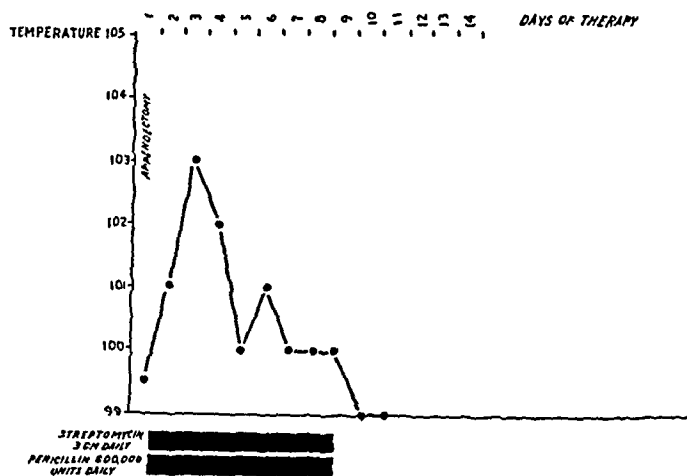
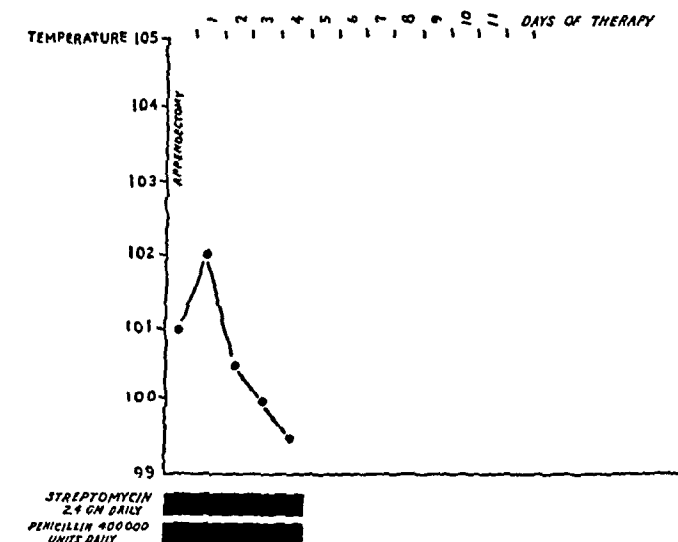


FIG 2

FIG 1—Temperature chart in acute gangrenous appendicitis with perforation and abscess formation managed by operative intervention and combined therapy. The temperature fell immediately after operation and recovery was uncomplicated.

FIG 2—Temperature chart in ruptured appendicitis managed by operative intervention and combined therapy. Although large quantities of pus were found in the peritoneal cavity, the temperature established a downward trend within 48 hours of the institution of therapy, post-operative distention subsided rapidly, and recovery was uncomplicated.

STREPTOMYCIN THERAPY IN PERITONITIS

FIG 3

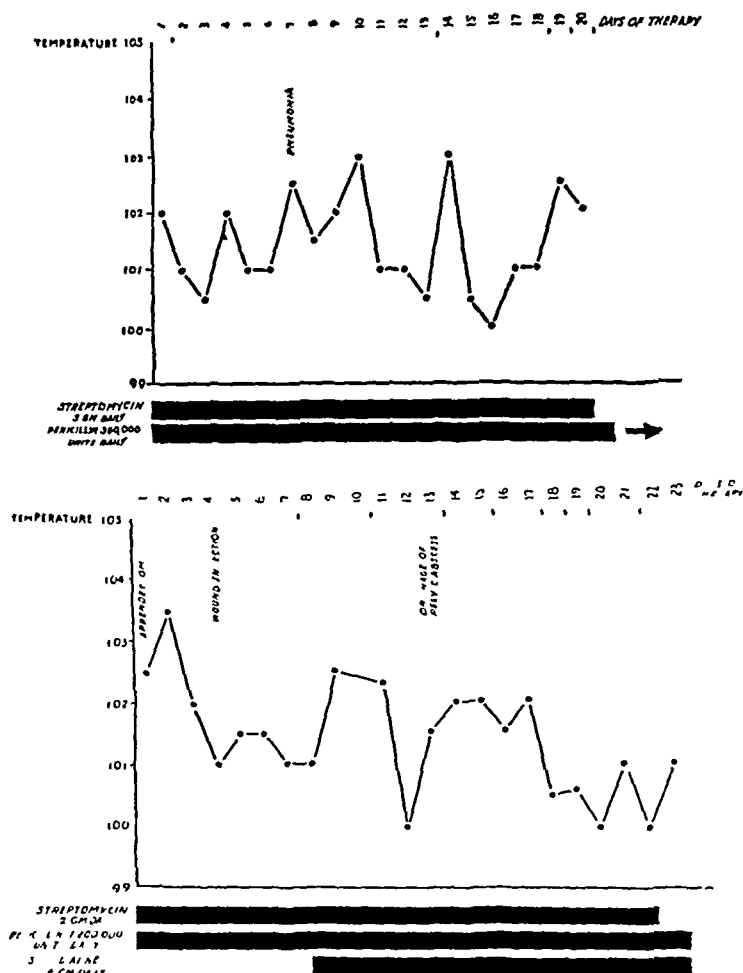


FIG 4

FIG 3—Temperature chart in severe trauma (gun-shot) with multiple perforations of stomach and small bowel and gross contamination of the peritoneal cavity. The postoperative course was stormy and temperature elevations continued although penicillin had been begun immediately after operation. Streptomycin was begun on the eighth postoperative day but was discontinued after 20 days because there was no appreciable response. The failure of antibiotic therapy in this case may be attributed to any one of several factors, including overwhelming sepsis, tardy initiation of streptomycin therapy, or failure, because of undrained pus, to achieve and maintain effective drug levels in local areas.

FIG 4—Temperature chart in ruptured appendicitis with spreading peritonitis, in which streptomycin and penicillin were begun immediately after appendectomy. Fever persisted, and on the fourth postoperative day a wound infection became evident. A pelvic abscess was drained on the thirteenth postoperative day. Although the reason for failure in this case is obscure, it is probably the overwhelming infection combined with failure to maintain effective drug levels in areas of undrained pus.

attributable to infection, (2) a definite regression, within 48 hours of the institution of therapy, of the pathologic process as demonstrated by reduction in the severity of the paralytic ileus and of the subjective symptoms of toxicity (3) absence of any of the postoperative complications common in peritonitis, such as pelvic and subdiaphragmatic abscess, fecal fistula and wound infection. A result was listed as negative if one or more of the criteria of a good result was not fulfilled. The assessment of results, it should be emphasized, was entirely from the standpoint of whether or not they could be attributed to the

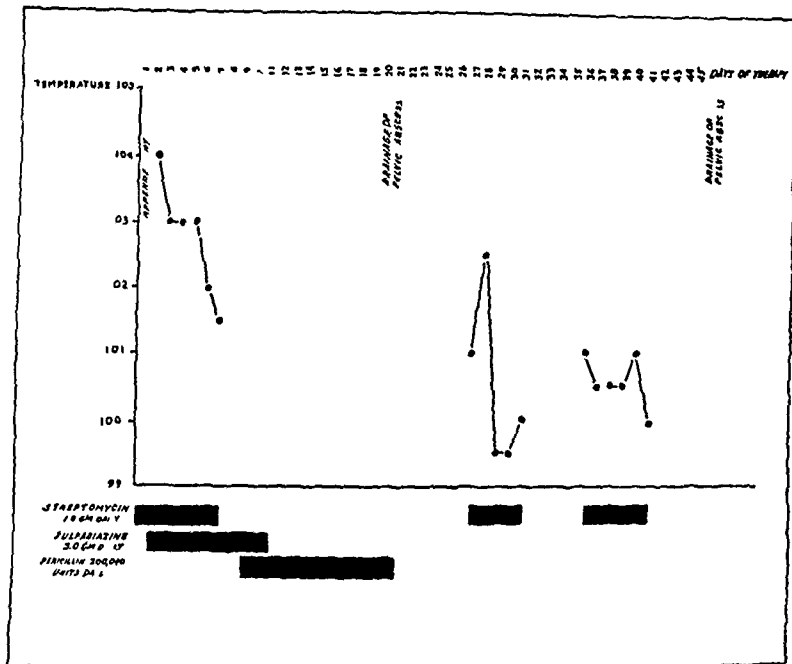


FIG 5—Temperature chart in perforated appendicitis with massive spreading peritonitis. Streptomycin and sulfadiazine were begun immediately after operation, and the response was satisfactory, but they were discontinued too soon and a pelvic abscess formed, which was drained on the twenty-first day. When another temperature elevation occurred on the twenty-seventh day, a short course of streptomycin was given, with favorable results, but the results were not so satisfactory when a similar episode occurred on the thirty-sixth day. A second pelvic abscess was drained on the forty-ninth day. The poor results in this case can be attributed to interruption of antibiotic therapy too soon after an initially favorable temperature response and, possibly, to the development of drug-fastness in the persisting bacteria.

use of streptomycin or of a combination of streptomycin and penicillin sulfadiazine.

Results in 12 of the 18 cases of peritonitis treated by streptomycin alone (Table I) were classified as *good* and six as *negative*, while in the 67 cases treated by combined therapy results were classified as *good* in 51 and *negative* in 16. The number of cases in single categories is not large enough to make the results statistically significant. On the other hand, clinical impressions and studies of individual cases (Figs 1-5) are not without value.

COMMENT

Generally speaking, cases of local peritonitis treated by a combination of drugs tended to show a better response to therapy than those treated by streptomycin alone. Of the failures in the group in which a combination of drugs was used, only 50 per cent were in cases of localized peritonitis, although when streptomycin was used alone, localized peritonitis accounted for 83.3 per cent of the failures.

When the data are investigated on the basis of the dosage of streptomycin, it is seen that the majority of the failures occurred in patients who received

TABLE II—*Evaluation of 22 Failures Receiving Simple and Combined Therapy in 85 Cases of Fecal Peritonitis*

Case No	No Temp Trend In 48 Hours	Ileus or Stormy		Complication Abscess etc	Inadequate Dosage	Local Tissue Causes	Overwhelming Sepsis Treatment Late
		Subjective State 48 Hours	State 48 Hours				
9	+	+				+	
12	+					+	
21		+		+	+		
33	+	+				+	
34	**	**		**	+	+	+
37*	+	+		+			+
38*	+					+	
41a	+	+		+			+(?)
43a*				+		+	+
48	+				+	+	
55	+	+		+	+		+
62	+				+		
64		+		+		+	+
65	+			+	+		+
71*	+	+			+	+	+
72				+		+	+
74*	+					+	
81	+	+					+
98		+				+	+
100*	+				+	+	
107	+	+		+			+
124		+		+		+	

* Case treated with streptomycin alone

** Indeterminate

2 Gm or less per day, which suggests that the chances of antibiotic failure are increased when the dosage is low. In the cases in which results were good, the temperature elevations persisted for an average of 9.6 days when combined therapy was employed against 13.5 when only streptomycin was employed.

An analysis of the 22 negative results following antibiotic therapy establishes certain possible explanations for the unsatisfactory response in these cases (Table II). Multiple causes were evident in several cases, just as a multiple lack of response was evident in several cases.

CONCLUSIONS

Statistical conclusions are not possible from the analysis of the 85 cases of fecal peritonitis presented in this communication and treated with strepto-

mycin alone or in combination with other drugs. Clearcut trends, however, permit the following impressions:

1 In early spreading peritonitis in which the infecting organism originates in the gastrointestinal tract, combined treatment with streptomycin and penicillin seems to offer no significant advantage over streptomycin alone. In the management of localizing lesions, on the other hand, combined therapy seems superior.

2 On empirical grounds, the optimal dosage of streptomycin, whether the drug is used alone or in combination, seems to be at least 2.5 Gm. daily.

3 After 48 hours it is usually possible to predict, with fair accuracy, the success or failure of streptomycin therapy.

4 The optimum course of therapy is seven to ten days. Administration of streptomycin should be continued for at least 48 to 72 hours after the temperature returns to normal, to prevent the development of an escape phenomenon.

5 An analysis of the response to antibiotic therapy in peritonitis is attended with difficulties. If such an investigation is undertaken, minimum information necessary for an adequate analysis consists of accurate temperature and pulse curves, notations as to the blood and electrolytes administered, periodic estimates of the nutritive and accurate notations of the return of bowel activity. Data are also necessary as to the condition of the skin wound and the results of rectal examination for possible abscess-formation.

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COMPLETE DUPLICATION OF THE LARGE BOWEL TREATED BY SUBTOTAL COLECTOMY*

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Complete duplications of the large bowel are exceedingly rare. The purpose of this paper is to record a case of complete duplication and the method of treatment in this instance. One case of triplication has been recorded.¹ Ombredanne,² Bar,³ Aitkin⁴ and Griess⁵ have reported cases of complete duplication. The duplication reported in this paper resembles that of Aitkin in that the terminal ileum was also double and demonstrates that the duplication may involve both ileum and colon (Figs 1 and 2).

CASE HISTORY

A. M., male. Age 4½ years. Admitted to the Children's Memorial Hospital on October 16, 1947.

The patient's chief complaints for the four months prior to his admission were the passage of fecal contents and gas per urethra, frequency and dysuria, and painful bowel movements. Since birth the child had experienced alternating periods of constipation and frequent bowel movements. When constipated, the abdomen became enlarged. The symptoms of recto-urinary fistula for four months prior to admission were the precipitating cause of hospital admission.

On physical examination the abdomen was protuberant and there was a mild degree of diastasis recti. On rectal examination a mass could be felt about the size of a lemon one inch within the anal orifice and anterior to the rectum. Within the mass small movable "stones" were felt to click together on palpation. It was thought that these were bladder calculi and a flat plate of the abdomen appeared to support this contention. However, they later proved to be fecaliths in the blind end of the duplication. The urine contained frank fecal contents and indicated that there was a fistula between the urinary tract and the bowel. Cystoscopic examination revealed gross fecal contents in the bladder and the examination was unsatisfactory in localizing the exact location of the fistula.

TREATMENT

The first operative procedure was to perform a transverse colostomy by the Wangenstein method (Fig 2-1) as a preliminary to localization and treatment of the recto-urinary fistula. When the colostomy was opened 48 hours later, the colon was found to contain a double lumen at this site. This was the first indication that a duplication of the colon was present. Subsequent cystoscopy demonstrated the urinary fistula to be between posterior urethra and rectum.

A perineal approach to the recto-urethral fistula was made (Fig 2-2), and the small fistulous tract was successfully divided and turned in at each end. At this time several firm fecaliths were removed from the termination of the duplicated colon. These had been previously palpated through the rectum and were thought to be bladder calculi. Two weeks following this

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procedure, the catheter was removed from the urethra and there was no recurrence of the fistula.

Four weeks later, a laparotomy was done through a left paramedian incision and a careful abdominal exploration was made. The entire colon, together with five inches of terminal ileum, appeared to be duplicated to within one inch of the anal canal. There were two appendices. Whether this duplication was continuous or segmental could not be ascertained at this

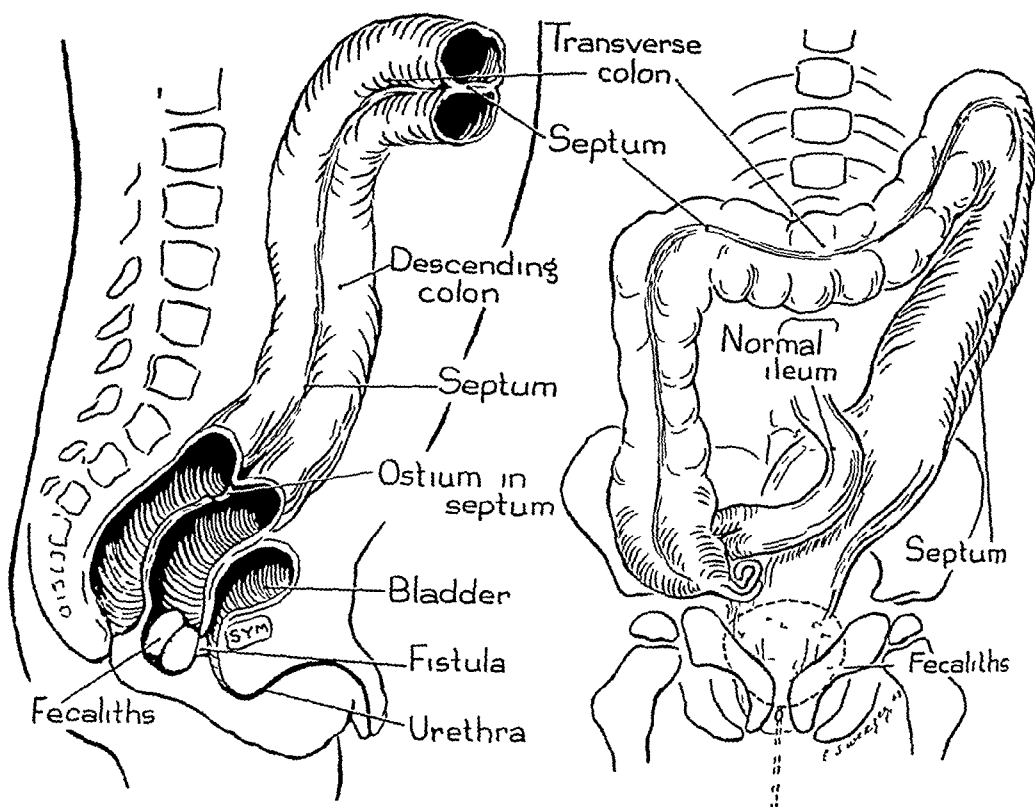


FIG. 1

time. A rectal tube was introduced through the anus to establish which colonic lumen communicated with the anal canal. Then the terminal ileum was anastomosed to this lumen at the rectosigmoid junction (Fig. 2-2).

Two weeks following this operation a subtotal colectomy was carried out, removing the duplicated terminal ileum and the entire colon as far as the rectosigmoid, about one inch above the previous ileorectosigmoidostomy (Fig. 2-4). In order to preserve a rectum, the double-barrelled stump of rectosigmoid was brought out to the skin surface and a crushing clamp was applied to the spur to convert the remaining duplication of the rectum into one chamber, similar to the method of breaking down a Mickulicz colostomy spur.

COMPLETE DUPLICATION OF LARGE BOWEL

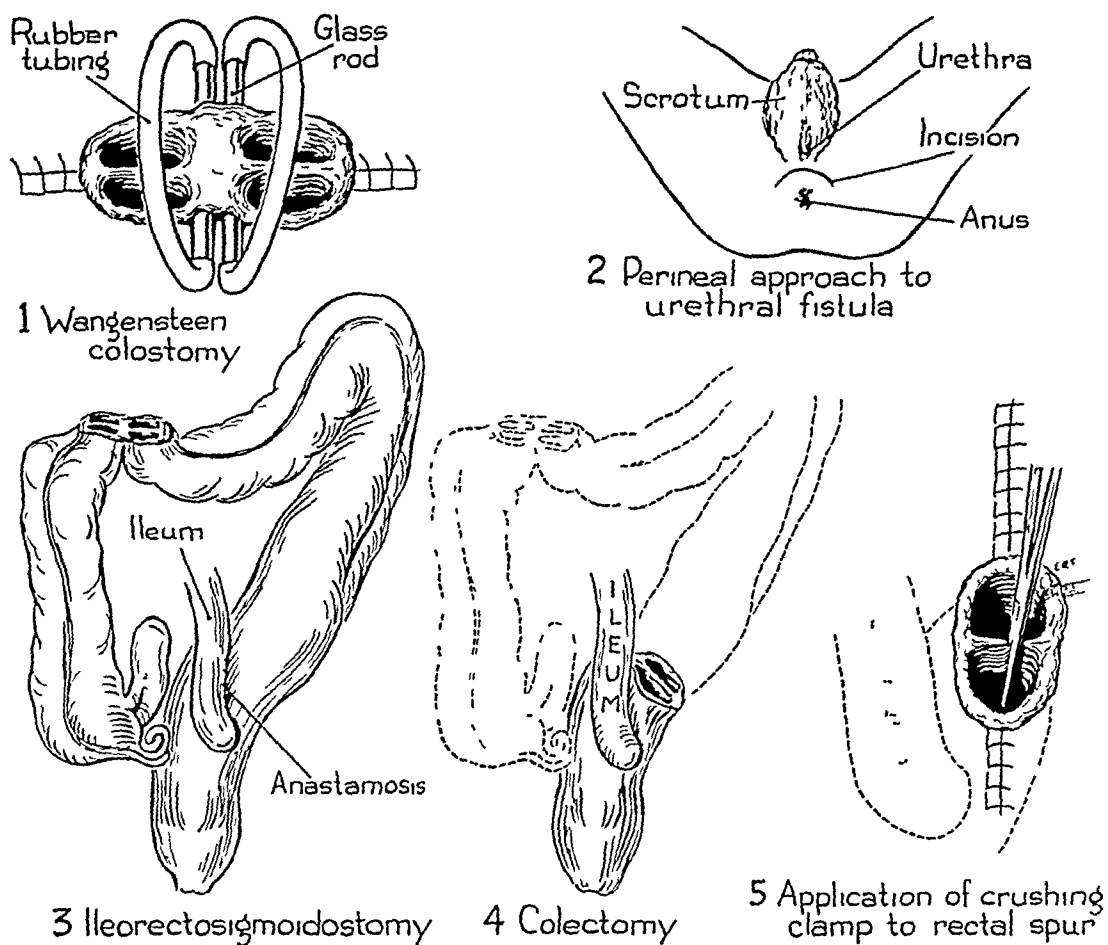


FIG 2



FIG 3—Bowel removed at operation

After the spur was completely crushed by three applications of the clamp to the septum (Fig 2-5), the colostomy was closed and the abdominal wall sutured

The patient was discharged 12 days after the last operation, on March 18, 1948, at which time he was having one to two soft-formed stools daily

COMMENT

Until the operative specimen was removed, it was impossible to determine the exact extent of the duplication and whether or not there were blind segments along its course. The presence and number of communications between the duplication and

the colon were not known. Barium examinations were inconclusive in answering these questions and it was for these reasons that it was thought wise to perform a subtotal colectomy.

On examining the operative specimen, the duplication was found to be complete, as shown in Figures 2 and 3. A small orifice connecting the two lumina was demonstrated in the rectosigmoid, just above the point of resection. This was the only communication between the two colons and meant that the duplication below this ostium was a blind pouch in which gastrointestinal contents accumulated, resulting in the formation of fecaliths (Fig. 1). The fecaliths which were removed from this reservoir were of a stony-hard consistency and the nuclei of two of them proved to be plum stones. Since the symptoms of urethral fistula had been present for only five months prior to the patient's admission, it is possible that this fistula may have been caused by ulceration of one of these stones into the posterior urethra.

The walls of the two colons were intimately blended and the picture was that of a median septum in a large colon, rather than two distinct colons (Fig. 2). All layers were complete, both in the duplication and in the normal bowel. The blood supply was a common one, which is the usual arrangement,⁶ and any attempt to separate the two parts would have been impossible. Until a rectal tube was introduced beyond the blind end of the duplication, it was impossible to tell which was the duplicated portion and which proceeded to the normal anal orifice.

The problem of preserving a rectum and, at the same time, eliminating the duplication, was difficult, but was solved by the repeated application of a crushing clamp to the rectal septum.

SUMMARY

1. A case of complete duplication of the colon with urethral fistula is described.

2. The method of treatment by subtotal colectomy with preservation of the rectum is described and illustrated.

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PRIMARY CARCINOMA OF THE DUODENUM

REPORT OF A CASE SURGICALLY RESECTED*

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PRIMARY CARCINOMA of the duodenum is regarded as a rare lesion. This is particularly true if care is taken to eliminate those tumors arising in the biliary papilla and the pancreatic or bile ducts leading into the ampulla of Vater.

The reported instances in which such primary lesions of the duodenum have been successfully resected surgically are indeed very few. An idea of the order of their frequency may be obtained from the following. Brunschwig and Tinsoliz¹ found, in a review of the literature up to 1942, seven instances of resection for suprapapillary carcinoma with four patients surviving the operation and, up to 1945, 16 resections for intrapapillary carcinoma with four patients surviving the procedure for a year or longer. Berger and Koppelman,² likewise, in a careful review, found, in all, 76 instances in which carcinomas of all portions of the duodenum had been resected with an over-all operative mortality of 31.6 per cent and a five-year survival rate of only 5.2 per cent.

With the increased attention directed at lesions in and near the head of the pancreas in the past decade under the impetus of the work of Whipple and his associates, and the perfection of surgical technics for their removal, the number of successfully resected cases as yet unreported is probably appreciable. Nevertheless, "The number of primary neoplasms of the duodenum seen by any one operator being limited, experience has not yet been sufficient to warrant general conclusions in regard to the surgery of these growths."¹ It is to add to the information on this subject that the present case is being reported.

CASE REPORT

The patient is a 60-year-old white male hospitalized on March 31, 1948, with a three-week history of painless jaundice, pruritis and hepatomegaly. This illness followed by one month recovery from an upper respiratory infection. There was no nausea or vomiting and stools were normal in color. His urines were dark. There was a 15-pound weight loss over a six-months' period. Past history included hospitalization in 1941 for intermittent fever and chills, at which time a liver enlarged four fingerbreadths below the costal margin was found on physical examination, and a gallbladder series, a gastrointestinal series and a barium enema were reported by the roentgenologist as normal. This was followed by a second hospitalization six months afterwards, during which time

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the patient developed a right upper quadrant mass and pain in that region while in the hospital. Operation on November 5, 1941, was performed for the removal of a dilated thickened gallbladder, which did not contain stones and which was reported pathologically as showing chronic cholecystitis.

Physical examination on the present admission revealed a well-developed and only moderately well-nourished, jaundiced white male appearing acutely and chronically ill. Examination of the head and neck, and the heart and lungs, was not remarkable. Blood pressure was 130/80. The right upper quadrant scar was well healed. The liver was palpable four fingerbreadths below the costal margin in the midclavicular line. The abdomen was otherwise not remarkable, nor was rectal examination.

Laboratory Studies Serology was negative. Hemograms showed a white-cell count of 13,150 with 60 per cent neutrophils, 31 per cent lymphocytes, 7 monocytes and 2 basophils, a red-cell count of 4.2 million and a hemoglobin of 13.7 grams. Fasting blood sugar was elevated to 180, urea nitrogen was 19, total proteins 6.8 grams, with albumin and

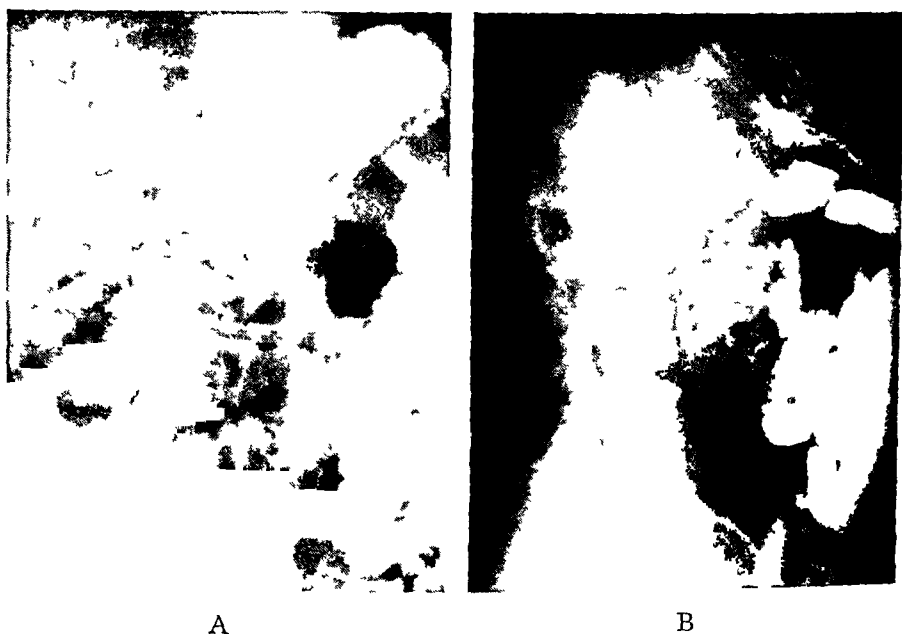


FIG 1 (A) Anteroposterior, (B) Lateral roentgen rays, showing an infiltrating lesion invading the descending duodenum with suggestive proliferative changes.

globulin fractions of 3.9 and 2.9 grams, respectively, and the icteric index was 45. Serum phosphatase determinations ranged between 10 and 18 Bodansky units, the van den Bergh reaction was direct positive and the cephalin-flocculation test was reported as 1 plus. The stools contained bile pigments in varying amounts and several specimens were positive on chemical examination for occult blood. Urinalyses were not remarkable except for variably positive reactions for bile and urobilinogen.

Roentgen studies included a gastro-intestinal series, which showed "widening of the duodenal loop with indentation on the medial and anterior wall and effacement and partial destruction of the mucosa in the second and third duodenal segments, with a shelf like zone in the lower half of the descending duodenum and in the third duodenal segment. The stomach and the duodenal bulb appear normal. There is no retention of barium after four hours." Differential diagnosis was thought to lie among carcinoma of the duodenum, carcinoma of the biliary papilla and carcinoma of the head of the pancreas (See Fig 1).

Duodenal drainage was performed and showed gross blood in the specimen. Adequate quantities of pancreatic enzymes were present.

Operation was performed on April 20, 1948. A localized tumor mass confined to the duodenum was found (Fig 2). The distal portion of the stomach and the duodenum around to the superior mesenteric vessels, together with the head of the pancreas, were resected. The distal duodenal segment was closed and an anticolic, antiperistaltic loop gastrojejunostomy (Polya type) was performed. Pancreaticojejunostomy and cholecystojejunostomy were carried out in that order, distal to the gastrojejunal anastomosis. The biliary anastomosis was drained.

The *postoperative course* was complicated by variably profuse biliary drainage with some of the bile getting into the intestinal tract. There was also intermittent obstruction at the gastrojejunal stoma associated with several periods of alkalosis. Although the gastrojejunal obstruction was proved to be incomplete by roentgenologic examination, a second procedure was carried out on June 10, 1948, with an anterior gastro-enterostomy being performed. Following this second operation, the patient's nutritional state improved considerably, with marked increase in weight and strength. The biliary fistula continued to drain in variable amounts for a period of five months following the original procedure but gradually closed down. The patient was seen February 22, 1949, and was in excellent physical condition. His biliary fistula had closed. He was last seen June 12, 1949.

The *pathologic report* was as follows: "The specimen consists of a previously sectioned piece of small intestine 18 cm long and 5 cm in circumference. Eccentrically located is a fungating mass in the mucosa which reaches a maximum longitudinal diameter of 7.5 cm, a maximum transverse diameter of 4.5 cm and an elevation of approximately 3 cm. There are two orifices in this mass which, when opened, continue into ductlike structures, neither of which appears grossly bile-stained. The serosal surface is pale pink and moderately injected. Attached to the serosal surface in the vicinity of the previously described tumor are soft, discrete, smooth-surfaced nodules whose surfaces are pale pink to red, and whose cut surfaces are yellow. There is also an irregularly shaped piece of tissue which is pale pink and nodular (pancreas), it is 6.5 cm long and 3.5 cm at its widest and 0.8 cm at its thickest" (See Fig 2).



FIG 1 (C) Oblique roentgen ray showing an infiltrating lesion invading the descending duodenum with suggestive proliferative changes

The *microscopic diagnoses* were (1) adenocarcinoma of the duodenum (descending portion), (2) fibrosis of the pancreas, and (3) regional lymph nodes free of tumor (See Fig 3).

The *incidence* of carcinoma of the duodenum is generally regarded from collected autopsies as being about 0.03 per cent. This represents about 0.3 per cent of all intestinal cancers,⁷ and approximately half of the cancers of the small intestine. If consideration is limited to the carcinomas, then it represents three-fourths of the carcinomas of the small intestines, the duodenum being the only portion of the small bowel in which carcinoma predominates.⁷ Howard,⁸ reviewing the literature in 1943, was able to find 55 cases of primary carcinoma of the duodenum in 117,433 collected autopsies; he carefully excluded cases of carcinoma of the pancreas and of the biliary papilla. In

their excellent critical review, Berger and Koppelman, in 1942, brought the collected cases considered authentic by Lieber, Stewart and Lund in their three papers^{10, 11, 13} up-to-date. They found a total of 77 acceptable cases of suprapapillary tumors, 251 of peripapillary lesions and 58 infrapapillary carcinomas



FIG 2—Gross specimen. Markers are inserted through the common bile duct and the main pancreatic duct. The head of the pancreas is not shown.

Dixon and others⁴ calculated that, by 1946, 718 cases had been reported, but only 433 of these were acceptable as true duodenal carcinomas.

The *age incidence* in carcinoma of the duodenum is slightly higher than in carcinoma of other parts of the small intestine. The tumors occur most commonly during the sixth decade and are extremely unusual before the age of forty. Figures reporting sex incidence are conflicting and indecisive.

Carcinomas of the duodenum are generally *classified* in three groups,

pending upon their anatomic relation to the biliary papilla (1) those proximal to the papilla, (2) those in the region of the papilla, and (3) those distal to it. The tumors in the region of the papilla are generally believed to be the most frequent and those distally to be least common, but this opinion is open to question as the former group may include instances in which the neoplasm was not truly primary in the duodenum.

From the *gross pathologic* point of view, the tumor usually takes one of two forms: either polypoid or stenosing. The latter type predominates.

The suprapapillary tumors probably bear no relationship to pre-existing duodenal ulcers inasmuch as they do not generally occur in the area in which peptic ulceration is most commonly found. They manifest themselves chiefly by obstructive phenomena.

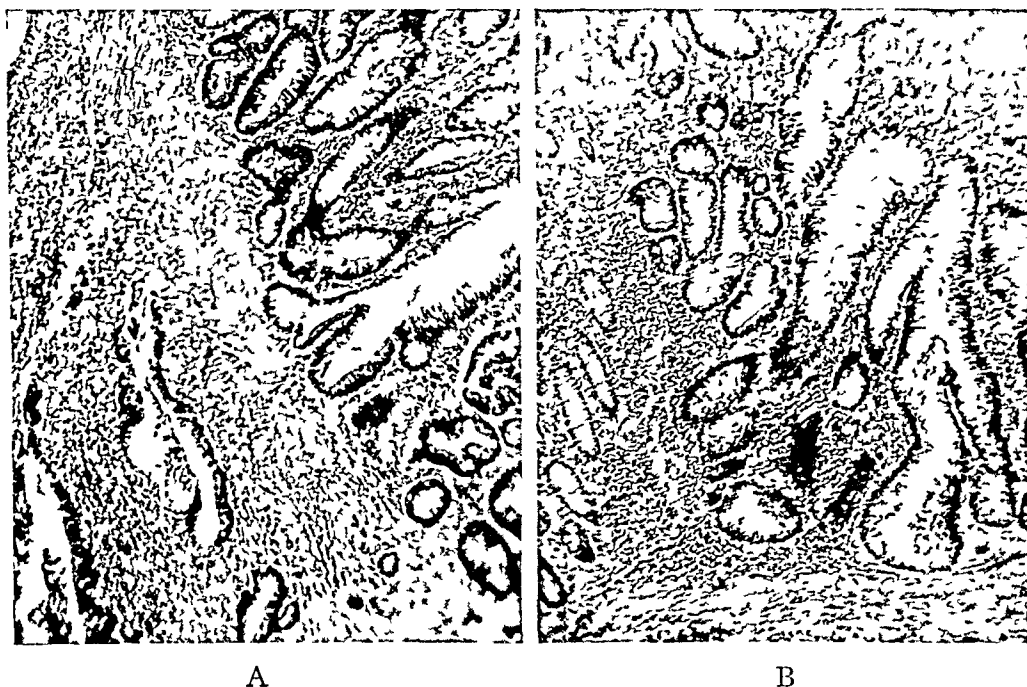


FIG 3—Photomicrograph (A) Tumor glands are seen infiltrating into the submucosa. (B) The transition from normal duodenal mucosa to malignant epithelial glands may be seen from left to right.

Carcinomas of the second portion of the duodenum usually arise closely adjacent to the biliary papilla. They are generally papillary growths and sometimes distinguished with difficulty from carcinoma in and around the ampulla. Howard quotes Pic's differentiation of the two forms (with which Ewing⁶ concurs), and it is worth repeating. Carcinomas of the papilla "as a rule, constitute circumscribed tumors that occupy only a portion of the intestinal wall and consequently resemble, in this respect, carcinomas that are situated in the head of the pancreas itself, whereas, true duodenal carcinomas show the same tendency that is so common in other forms of intestinal carcinoma, namely, to develop in an annular or cylindric manner and so involve the whole circumference of the intestine." The validity of this observation in early cases will rest upon the analysis of reports on surgically resected specimens.

Among the infrapapillary tumors, the scirrhous annular type composed of firm white tissue, is somewhat more frequent than the soft polypoid pedunculated, medullary type.⁵ Ulceration is common and stenosis is quite frequent.

Histopathologically, the tumors consist of cylindrical-cell adenocarcinoma derived from intestinal mucosa. Many cases are difficult to separate from primary carcinoma of the pancreas,⁶ and speculation has even been offered as to the possibility of carcinoma arising from aberrant pancreatic tissue in the duodenal wall. Duff and others⁵ describe the annular tumors as having abundant stroma and few cells, while the medullary lesions have scant stroma with abundant cells. Hoffman and Pack⁷ point out that carcinomas of the ampulla of Vater have the histologic characteristics of bile-duct tumors, a point of differentiation from the peripapillary lesions.

Metastasis from these tumors is believed to occur rather late, with the regional lymph nodes bearing the brunt of the spread. However, early and fairly extensive metastasis has been described.

Carcinomas of the duodenum are so uncommon that they are rarely considered in the *differential diagnosis* of abdominal complaints, or even of upper abdominal tumors. It is only recently that ante-mortem diagnosis has been made with any degree of frequency. The tumors are apt to be slow and very insidious in their growth. In the first and third portions of the duodenum they manifest themselves chiefly by obstructive phenomena which are usually attributed to other causes, even when demonstrated roentgenographically. Abdominally palpable tumor masses are most unusual.

Jaundice is seen chiefly with the peripapillary tumors, but may occur with the other types.⁴ Whereas Berger and Koppelman, and Ewing state that with peripapillary carcinoma it is an early and constant symptom, Howard claims that even in this location jaundice occurs but rarely, and then as a preterminal event. This last is partly confirmed by Dixon's series, in which it occurred in only four of 15 periampullary carcinomas and then it was usually a late manifestation. At any rate, "the jaundice in these cases is less severe and persistent than with carcinoma of the ampulla. Even in advanced cases the occlusion of the duct may be incomplete."⁸

Clinical diagnosis is at best difficult and will probably be most successfully approached through the roentgenologist. This was demonstrated in the last 20 cases reported by Dixon and others, in all of which a reasonably correct diagnosis was made from the roentgen findings. Duodenal drainage with chemical and microscopic analysis of the duodenal contents is an infrequently used but valuable adjunct to correct diagnosis. Kaiser⁹ criticizes the accuracy of our ante-operative measures and claims that even at operation differentiation of lesions obstructing the biliary passages is difficult. He offers cholangiography at the operating table as a solution. More extensive experience by other investigators is required for evaluation of the accuracy of this method in differentiating among the various causes of common-duct blockage.

The *surgical treatment* of tumors of the duodenum has been considered by Brunschwig and Tinholiz under three headings (1) resection of the tumor and the involved portion of the duodenal wall, (2) resection of a segment of the duodenum and an adjacent segment of the head of the pancreas, and (3) pancreaticoduodenectomy, resecting the entire duodenum and the head of the pancreas. Analyzing the surgical results up to 1942 Berger and Koppelman report that of the suprapapillary tumors 27 were treated surgically with only 7 lesions proving resectable and with an operative mortality among the latter of 43 per cent. There were 136 instances of peripapillary carcinoma subjected to operation with only 58 proving resectable and this with an operative mortality of 29.3 per cent. Among 64 purely palliative procedures the operative mortality was 73.5 per cent. There were 33 cases of infrapapillary carcinoma operated upon. 11 proved resectable with an operative mortality of 33 per cent, the mortality for those cases having only exploration or a palliative procedure was 90 per cent.

In 1937 Hoffman and Pack reviewed 18 cases collected from a number of hospitals. 12 of which were operated upon. An attempt at removal was deemed possible at that time in only one instance, with a postoperative death. They describe three of their lesions as being supra-ampullary, seven as peri-ampullary and six as infra-ampullary. Cohn,³ in 1944, described two cases of supra-papillary carcinoma diagnosed preoperatively but failing to survive more than three months postoperatively. Only one of the cases was resectable. Shallow, Eger and Carty,¹² in 1944, were able to collect from the world literature only 12 unquestionable cases of primary carcinoma of the third portion of the duodenum in which resection was done. Of these, five were dead and six well, the result in the remaining case being unstated, the longest survival was six years postoperatively. Duff, Foster and Bryan⁵ described an inoperable case of infra-ampullary, scirrhous carcinoma with almost complete lumen occlusion that survived seven and one-half months after exploration and sidetracking without resection. Dixon and others report that among their 45 cases nine were resectable, 28 had palliative procedures and eight were only explored. Of the operable cases four were radical resections, four segmental and one local, with a mortality of 22 per cent. Brunschwig reviews three cases of his own, with one each of local resection, segmental resection and pancreaticoduodenectomy.

Howard's study showed an average survival of from six to 14 months in unoperated cases of carcinoma of the duodenum taken as a group. Two surveys^{1, 2} touching on the operative survivals have already been mentioned.

This survey of the literature, by no means complete, serves to give one an idea of the frequency with which these tumors of the duodenum have been found and how often subjected to surgery. There are, undoubtedly, at the present time throughout the world many surgically treated cases as yet unreported. Valid criteria for diagnosis, resectability, choice of surgical procedure and prognosis with treatment awaits the compiling of sufficient data on the subject to lend themselves to statistical analysis.

SUMMARY

1 A case of primary carcinoma of the second portion of the duodenum subjected to pancreaticoduodenectomy is presented

2 An idea of the types and frequencies of carcinomas of the duodenum and attempts at resection is given

3 There is a need for further reports on the subject, particularly the results obtained within the past five years

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ISOLATED FRACTURE OF THE ATLAS

REPORT OF TWO CASES*

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ISOLATED FRACTURES of the atlas are rarely seen by either the surgeon or the radiologist. Two cases, occurring within a few months, have alerted us to believe that this condition may occur more frequently than is suspected. Increase in the speed of travel and subsequent accidents should show an increase in the number of cases of this type. These injuries are usually fatal. We wish to report two cases that survived.

FREQUENCY

The first case to be reported in the literature was described by Sir Astley Cooper in 1822 following a postmortem examination. A review of the literature reveals the following statistics:

TABLE I

Author	Year	No. of Cases Reported
Jefferson ^{2,3}	1927	20
Plaut ¹	1937	20
Sinberg & Burman ⁴	1940	1
Wortis & Sharp	1941	2
Hatchette ⁵	1941	1
Crooks & Berkett ⁷	1943	3
Hinchey & Bickel ⁸	1945	6
Johns ⁹	1945	1
Authors Cases	1946	2
		—
		56

The infrequency of this lesion can best be illustrated by the report of Crooks & Berkett who, in reviewing a total of 39,479 fractures at the Nottingham General Hospital and Chesterfield Royal Hospital, found a total of 618 fractures of the vertebrae of which 59 involved the cervical vertebrae and that 73 per cent of these had evidence of injury to the spinal cord or root. Seventy-five per cent of those with neurological signs died.

A review of 246 consecutive cases of fracture of the vertebrae during a 20-year period beginning in January, 1927, at the Reconstruction Hospital Unit, showed 33 cases involving the cervical vertebrae of which two involved the atlas, approximately 6 per cent of all cervical fractures or 0.8 per cent of all fractures of the vertebral column.

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ANATOMY

The atlas is at the level of the hard palate and is protected from direct violence by the skull, mastoid process, and maxilla. Even though the cervical vertebrae are most exposed to injury because of their greater mobility and junction to parts that are more fixed, the head and thorax, one would assume that direct violence to the head would produce more fractures of the atlas. However, its chief provisions for protection are the number of cervical vertebrae and their joints which allow movement without serious weakening.

Jefferson, quoting the work of Wagner and Stolper, and Smith, showed that fracture of the atlas could not be produced in the cadaver.

PATHOGENESIS OF FRACTURE

Because of its anatomical and functional characteristics, the forces which produce fractures in the other vertebrae do not apply to the atlas. It is evident that fixation of the spine and head by muscular contraction in association with trauma is one of the primary causes. The transmission of force with the skull in flexion is carried through the lateral masses and produces fractures usually in the fifth or sixth cervical vertebra. Fracture of the skull is more likely to result than fracture of the atlas.

One can summarize the different methods for fracture of the atlas

- 1 Pressure of the dens against the anterior arch (Fig 1)
- 2 Pressure between skull and axis (Fig 2)
- 3 Leverlike action on the posterior arch (Fig 3)

CASE REPORTS

Case 1 36842—H M is a 38-year-old white male who was injured by bumping his head on a windshield on February 7, 1946, at about 9 00 P M while riding in the front seat of an automobile which was struck by another. There was no history of unconsciousness. His chief complaint was severe pain in the neck. The patient was a diabetic under treatment for the past two years and also suffered from mild diabetes mellitus which was managed by a restricted diet.

The positive physical findings were a sluggish left pupil although both pupils were equal, regular, and reacted to light and accommodation. Although the neck could be moved in all directions, the patient guarded it. There was considerable tenderness throughout the cervical spine.

Radiographically there was a fracture through the left portion of the posterior arch of the first cervical vertebra with slight narrowing of the intervertebral space between the first and second cervical vertebrae on the left side (Fig 4).

The first six days post-trauma, the patient was kept in bed in hyperextension. A minerva-type cast was then applied. On April 18, 1946, 70 days post-trauma, a metal brace was substituted for the cast. Repeated radiographic examinations have shown little or no changes at the site of fracture. The brace was discarded 10 months post-trauma, and on the 13th month following injury there were no complaints referable to the neck.

Case 2 37215—W C is a 3½-year-old white male who was struck by an automobile on August 10, 1946. When brought into the hospital he was semi-conscious and responded only upon deep stimulation. The actions of the child indicated pain in the frontal region of the head and in the right hip. Physical examination revealed the child to be in moderate distress, with difficulty in respiration. There was grunting on expiration.

ISOLATED FRACTURE OF THE ATLAS

FIG 1

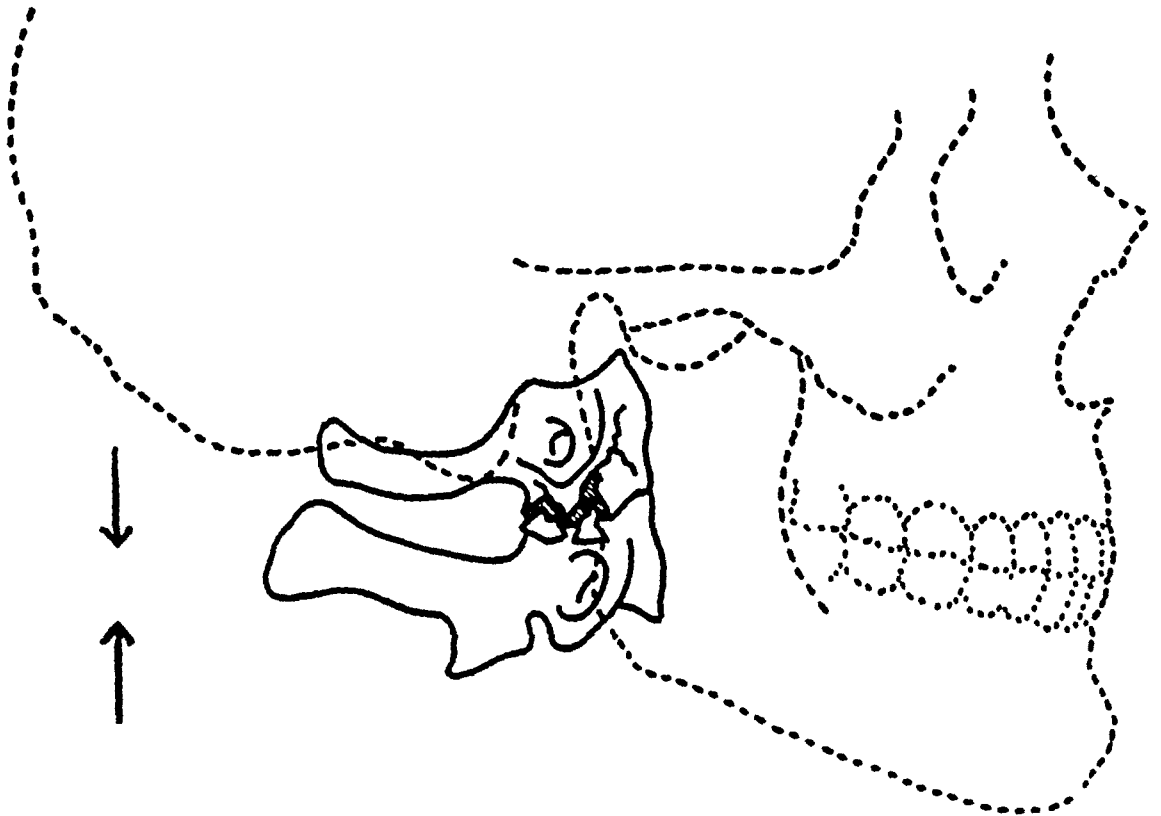
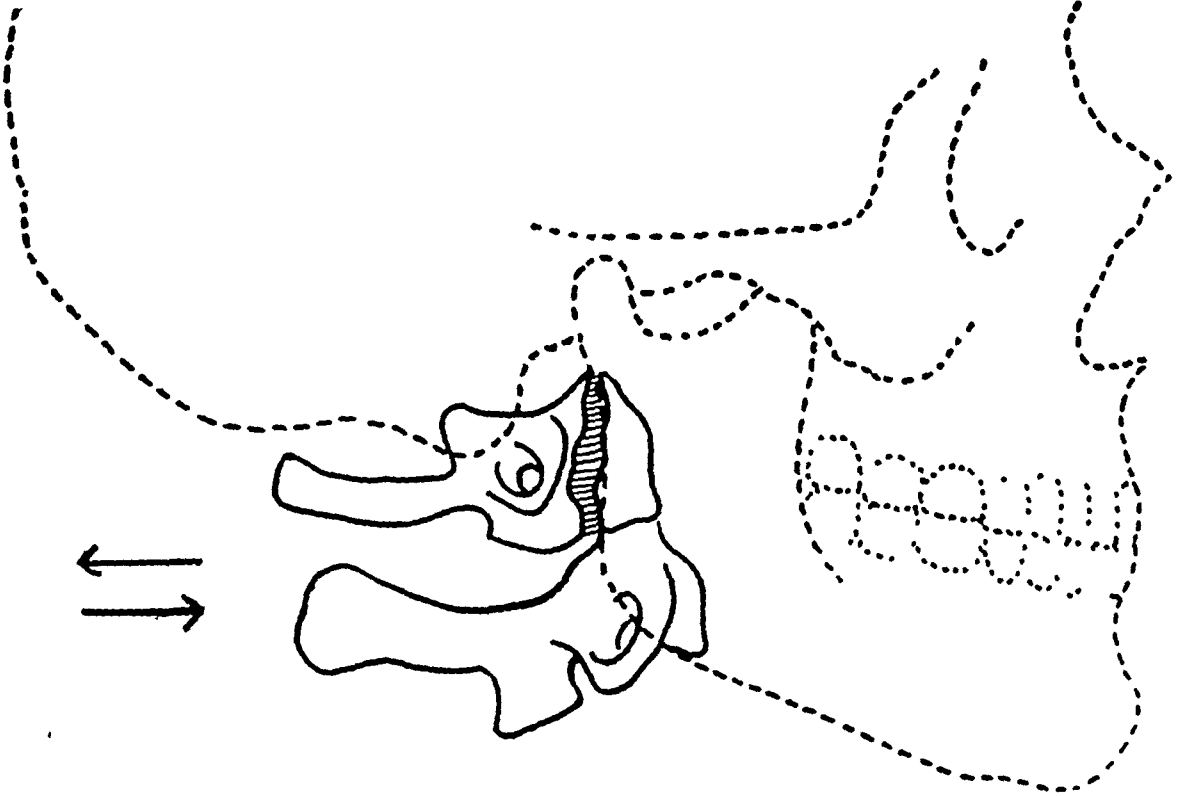


FIG 2

FIG 1 —Direction of forces necessary to produce fracture of the atlas with the dens against the anterior arch

FIG 2 —Direction of forces necessary to produce fracture when the pressure is between the skull and axis

FIG 3

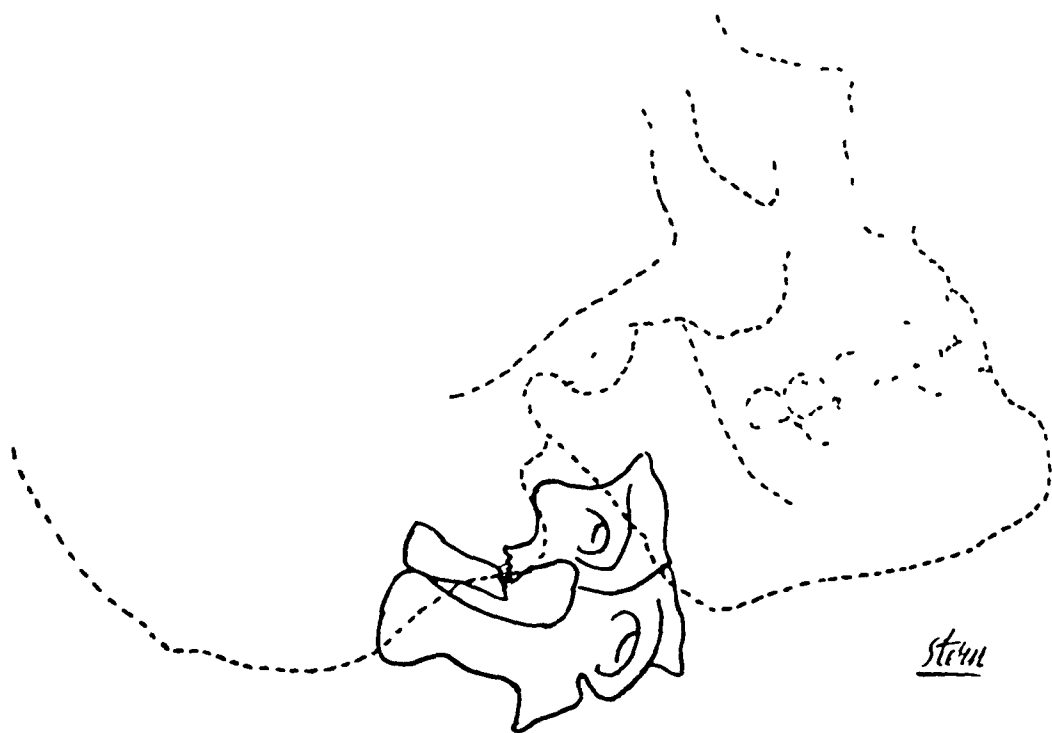


FIG 4

FIG 3—Illustrates the fracture of the atlas produced by the leverlike action on the posterior arch

FIG 4—Case 1—Radiograph taken upon admission revealing fracture through the posterior arch

ISOLATED FRACTURE OF THE ATLAS

ation A large hematoma was noted over the left forehead There were no voluntary movements of the head, passive motion elicited pain referable to the right ear (for the child cried and placed his hand over the ear)

Moderate tenderness over the right costovertebral angle with spasm of the abdominal muscles was found on the right side The right leg was flexed on the abdomen with the knee abducted Twenty-four hours after admission all physical signs of injury to the abdomen or thoracolumbar spine disappeared The child complained of severe earache in the right ear and difficulty in swallowing Otologic examination was negative

Roentgenologic examination of the cervical vertebrae revealed a fracture of the posterior arch of the atlas on the right side Neurological examination on the first day post-trauma was essentially normal A minerva-like cast was applied with the head in hyperextension On the twenty-fifth post-traumatic day there was evidence of weakness of both upper and lower right extremities Examination revealed a slightly flaccid right upper extremity, and we were unable to elicit deep reflexes Cerebrospinal fluid examination was normal Neurological consultation confirmed the impression of contusion of the spinal cord

Patient was discharged on the fiftieth day post-trauma with a steel and leather neck brace By the third month after injury there was no pain or deformity There was slight atrophy of the calf muscles of the right leg Six months post-trauma the collar was discarded and the patient discharged No residual defect was noted, and no atrophy could be determined

DIAGNOSIS

Fracture of the atlas should be considered when patients, following trauma, complain of stiffness and pain in the suboccipital region, inhibition of active flexion and extension, restriction to passive movements, difficulty in swallowing, and the sensation of food sticking in the throat For the technic of roentgenologic detection one is referred to the excellent papers of Plaut, and Anderson and Burgess

COMPLICATIONS

An analysis of Plaut's survey of isolated fractures of the atlas shows a mortality rate of 25 per cent If the above two cases are added to the previous cases noted in Table I, the mortality rate would be 17.8 per cent

Hemorrhage from the vertebral artery should always be considered where distention of the prevertebral fascial spaces occurs The difficulty in deglutition in Case 2 may be due to retropharyngeal distension

TREATMENT

Hyperextension and immobilization is the treatment of choice The period of disability varies with the type of fracture, site, and the age of the patient All cases reported previously by various authors seem to indicate that an uneventful recovery is to be expected if the patient survives the initial trauma

SUMMARY

- 1 Two cases of isolated fractures of the atlas are presented bringing the total reported in the literature to 56

- 2 The anatomy of the atlas is reviewed and the mechanism of fracture considered

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AN UNUSUAL EXPERIENCE WITH THE MILLER-ABBOTT TUBE^{*}

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FROM THE SANDERS CLINIC

INTUBATION of the gastro-intestinal tract by the use of the Miller-Abbott tube has proved definitely beneficial in certain types of obstruction. The procedure is advantageous in the preparation of patients for operation, as well as a means of conveying fluids and nourishment into the intestinal tract beyond the stomach. In some cases, unlimited patience on the part of both the operator and the patient is required to pass the balloon through the pylorus. After entering the duodenum, the tube may pass rapidly through the entire intestine. In two of our cases, the balloon protruded from the anus. Below is reported a case in which a rather unusual complication arose following the use of the Miller-Abbott tube. We have not seen a similar report in the literature.

CASE REPORT

C W B, a white male, age 63, was admitted to the hospital in August, 1947. Twenty years earlier, he had had a posterior gastro-enterostomy and cholecystectomy for multiple subacute perforating and bleeding duodenal ulcers and chronic cholecystitis with stones. The appendix had been removed at a previous operation. Aside from a few episodes of epigastric discomfort associated with a feeling of fullness and occasional vomiting, he seemed to get along fairly well following this operation. The latest attack had begun several weeks prior to his admission to the hospital. He had since found it necessary to restrict his diet to soft food and liquids, and within a few weeks had lost ten pounds in weight. At times, he had vomited large amounts, which gave him relief.

On roentgenographic examination in the hospital, the stomach was enlarged and its tone and motility were decreased. Only a little barium passed through the gastro-enterostomy. The duodenum was extremely dilated, especially in the first and second portions. On three-hour examination, approximately 80 per cent of the barium remained in the stomach. From this study, the patient apparently had an almost complete obstruction of the jejunum just distal to the gastro-enterostomy.

After adequate preparation, an operation was performed under spinal anesthesia. Extensive omental and intestinal adhesions were encountered in the upper abdomen, requiring considerable dissection to permit inspection of the posterior gastro-enterostomy. The first part of the jejunum just distal to the gastro-enterostomy was found almost completely obstructed by adhesions and angulation. The stomach and duodenum were enormously dilated, incident to this obstruction. The gastro-enterostomy stoma was ample, though a marginal ulcer was present. There was also some fixation to the colon and to the transverse mesocolon, as if the ulcer had partly perforated and was protected. The adhesions and the angulations of the upper jejunum were dissected free, restoring a normal intestinal lumen, and a bilateral vagal resection was done. It was believed that the obstruction had been overcome, and that the vagal resection would allow the gastrojejunal ulcer to heal.

The patient's immediate convalescence proceeded smoothly and he ate fairly well. On the twelfth postoperative day, however, he complained of pain in the upper abdomen and

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was troubled with nausea. The Levine tube was reinserted and suction applied. After several days he was again able to eat and his elimination was satisfactory. His further progress was uninterrupted, and he was discharged from the hospital at the usual time.

A few days later, his original symptoms returned, accompanied by distention, nausea and vomiting, indicating an obstruction at or just beyond the pylorus. Roentgenograms revealed considerable elongation and dilatation of the stomach, with dilatation of the duodenum as far around as the gastro-enterostomy. Apparently, the duodenal loop was almost completely obstructed. The efferent loop appeared normal. The obstructive lesion at the gastro-enterostomy stoma delayed gastric emptying considerably, though not completely. The three-hour film showed barium in the ileocecal region, a small amount



FIG 1



FIG 2

FIG 1—Miller-Abbott tube inserted for surgical preparation of a patient. Tube has passed through the stomach, the pylorus and the duodenum, and back into the stomach through the gastro-enterostomy, making almost three complete circles.

FIG 2—After attempts at withdrawal, the tube forms a circle about one-half as large as that shown in Fig 1. The first part of a knot has been formed by two loops of the tube within the stomach.

remaining in the distended duodenum. Another operation was obviously necessary, but because of the patient's weakness from inability to retain food, preoperative measures to improve his condition seemed advisable. It was thought that if a Miller-Abbott tube could be passed through the site of the obstruction, he could be fed by this means. The day after passage of the tube, fluoroscopy revealed that its tip had entered the small bowel via the pylorus. Liquid nourishment was therefore given through the tube at frequent intervals. Another roentgenogram made the following day showed that the tube

had passed, not only through the stomach and pylorus, but through the duodenum and back through the gastro-enterostomy stoma, making almost three complete circles (Fig 1) Its tip at this time was just beyond the stoma, apparently in the first portion of the jejunum It was decided that the tube should be withdrawn, and this was attempted, but without success Another roentgenogram was then made, which revealed that the loops had been drawn tighter, forming a circle about one-half the size of that shown on the previous examinations The tip lay in the region of the duodenal cap It was also found that the first part of an ordinary knot had been formed by two loops of the tube within the stomach (Fig 2) After three days, this situation was still unchanged The operation for release of the obstruction was therefore undertaken without further delay, removal of the tube being planned at the same time

On opening the abdomen, widespread omental and intestinal adhesions were again encountered, necessitating extensive and tedious dissection for exposure of the gastro-enterostomy The marginal ulcer which had been found at the previous operation was still present, and the surrounding tissues were even more edematous and fixed, causing obstruction of the jejunum at this point The gastro-enterostomy was disconnected and the marginal ulcer excised The Miller-Abbott tube, which had made three loops through the pylorus into the duodenum, thence through the gastro-enterostomy and back into the stomach, was divided into segments and removed A Levine tube was sutured to the remaining part of the Miller-Abbott tube, and this was withdrawn from above, allowing satisfactory placement of the distal end of the Levine tube into the jejunum The opening in the posterior wall of the stomach was closed, and the jejunal opening was sutured transversely, thus restoring the continuity of the tract and overcoming the obstruction

On the day following this operation, the Levine tube was clamped off for 20 minutes of each hour without causing the patient any discomfort The following day, it was clamped off for 30 minutes of each hour The patient was given liquids both by mouth and through the tube On the fifth postoperative day, the tube was removed and he was placed on a limited stomach diet As this was increased, he regained strength and was able to leave the hospital on the twelfth postoperative day He had no further difficulty thereafter, rather, he rapidly gained weight and strength and, when last seen 10 months postoperatively, had gained 50 pounds and had remained entirely free of symptoms

As stated in the beginning, we feel that the Miller-Abbott tube is definitely beneficial in certain cases From the experience reported above, however, it obviously should be used under careful supervision and with frequent fluoroscopic observations to determine the location of the tip of the tube in the intestinal tract This precaution is especially necessary in patients who have had some type of intestinal anastomosis

SPONTANEOUS INTERNAL BILIARY FISTULA

A REVIEW OF THE LITERATURE AND REPORT OF TWO CASES*

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THIS REPORT is presented to review the literature and describe two instances of spontaneous internal biliary fistula of entirely different etiology yet with identical symptoms and findings. These patients were in the hospital at the same time, and the diagnosis of spontaneous internal biliary fistula was made preoperatively in both instances.

ETIOLOGY AND PATHOGENESIS

Spontaneous gastro-intestinal biliary fistulas are attempts by nature to drain the chronically infected gallbladder. These fistulas are always secondary to other pathologic changes in the biliary tree. Gallstones are the provocative agent in 90 per cent of the cases, while perforating peptic ulcers are the offending agent in approximately 6 per cent. Other etiologic factors that make up the remaining 4 per cent are carcinoma of the gallbladder and of the biliary tree, abscesses in the biliary tree, and such rarities as echinococcus cysts. The formation is, for the most part, dependent upon an obstruction of the extrahepatic biliary-duct system. Small gallstones may be the causative agents by producing an obstruction of the cystic duct, following which empyema of the gallbladder with subsequent gangrene may develop. While this process is going on, with the production of a pericholecystitis and either a periduodenitis or pericolicitis, the intestine, small or large, becomes plastered to the infected viscus. If the gangrene continues, the stones rupture through the gallbladder wall and produce an abscess with necrosis of the intestinal wall and ensuing formation of a fistula. On the other hand, when a large stone is the causative factor, there is destruction of the gallbladder mucosa by pressure necrosis. With this occurs a concomitant cholecystitis and shrinkage of the gallbladder, accompanied by pericholecystitis and the formation of adhesions. The process of pressure necrosis, if not stopped by surgical intervention, will go on to erode the intestine and produce a fistula.

What is the outcome of these fistulas? They can either close spontaneously or produce serious disturbances in the hepatobiliary system. The formation of a fistula will intensify the hepatic dysfunction incident to the original biliary disease by producing cholangitis, hepatitis and obstructive jaundice. The reason for this is that the formation of the fistula follows obstruction of the common bile duct either because of the inflammatory reaction or the progression of the calculus down its mouth. As long as the common duct remains occluded there

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is no possibility of the fistula's closing spontaneously. Therefore, we can say that the formation of a spontaneous internal biliary fistula is in no way a cure for cholelithiasis, but an additional and dangerous complication.

INCIDENCE

Borman and Rigler¹ report 67 internal biliary fistulas in 30,000 autopsies. In reviewing 6,000 autopsies at Cook County Hospital, Davison and Aries² found seven cases of internal biliary fistula. Taylor,³ in his paper states that there is an incidence of 2.6 per cent of spontaneous internal fistulas in autopsies in which gallstones are found. Roth, Schroeder and Schloth,⁴ in a review of 10,866 autopsies, discuss finding 43 spontaneous internal biliary fistulas. In reviewing 2,000 cholecystectomies Kehi⁵ found 100 biliary fistulas. Peustow⁶ states that in all biliary-tract surgery the incidence of fistulas is 3.5 per cent. Hicken and Coray⁷ in their series have a slightly higher incidence, 4 per cent, while Feldman⁸ reports an incidence of 0.4 per cent.

In this paper we shall concern ourselves only with the spontaneous internal biliary fistulas between the biliary system and the gastro-intestinal tract, more specifically with cholecystoduodenal fistulas. Other biliary fistulas may extend upward into the pleural cavities or as far downward as the urogenital tract.

In a series of cholecysto-gastro-intestinal fistulas, reported by Hicken and Coray,⁷ 69 per cent were cholecystoduodenal, 26 per cent were cholecystocolic and 4.4 per cent were cholecystogastric. Courvoisier and Naunyn,⁹ in a series of 384 cases, reported 93 cholecystoduodenal, 49 cholecystocolic and 12 cholecystogastric. Judd and Burden¹⁰ reported 153 cases in which they found 117 cholecystoduodenal, 26 cholecystocolic and 6 cholecystogastric fistulas. Bernhard,¹¹ in his series of 109 cases, reported 56 cholecystoduodenal, 36 cholecystocolic and 12 cholecystogastric fistulas. In Peustow's⁶ series of 67 cases, 31 were cholecystoduodenal.

Spontaneous internal biliary fistula is found three to five times more commonly in women than in men.

It occurs in patients over 50 years of age and more commonly over 60 years of age. Both of our patients were women over 60 years old.

SYMPTOMATOLOGY

The symptoms of spontaneous internal biliary fistula are not distinguishable from those characterizing the parent pathologic condition. The formation of a fistula may result in a sudden cessation of the patient's complaints, more frequently the symptoms are intensified. Both our patients complained of right-sided abdominal pain and loss of weight of 20 to 30 pounds in a very short time.

There is usually a long-standing history of gallbladder disease with fever, jaundice and loss of weight. The duration of the symptoms averages approximately 10 years. The reason for the intensification of the symptoms is the development of a retrograde cholangitis and hepatitis due to the spilling of gastro-intestinal contents into the biliary tree.

The immediate dangers of a spontaneous internal biliary fistula other than the above-mentioned cholangitis and hepatitis are intestinal obstruction by the calculus anywhere from the duodenum to the ileocecal valve or an erosion into a blood vessel with the production of a severe hemorrhage

DIAGNOSIS

The diagnosis of spontaneous internal biliary fistula is made by roentgen ray examination or at operation

The roentgen diagnosis of this condition was first made by Hunt and Herbst¹² in 1915. The cholecystogram may be reported as showing a nonfunctioning gallbladder. On the other hand, a barium meal will reveal the presence of the barium and gas in the biliary radicles. Presence of gas in the gallbladder is indisputable evidence of internal biliary fistula. There are two other conditions which give the above findings, namely, an internal biliary fistula produced surgically and an incompetent sphincter of Oddi.

In a series of 21 cases presented by Tracey and McKell, Jr.,¹⁴ three fistulas were diagnosed preoperatively. Borman and Rigler¹ identified on roentgenray only 86 out of 267 fistulas. In both our patients the diagnosis was made by our roentgenologist preoperatively.

MANAGEMENT

There is great variation in the literature as to the management of the above-mentioned disease or syndrome. Minty¹⁷ states that if there is no cholangitis present, the fistula should be left intact rather than run the risk of submitting the patient to an external duodenal sinus. Hinchey¹⁵ is of the opinion that as soon as the diagnosis is made the fistula should be closed by operative measures. Hicken and Coray⁷ are also of the opinion that surgical intervention is of prime importance after the patients have been returned to fluid, electrolyte and protein balance. As can be noted, the management in both our cases was surgical. It is our firm belief that surgery is the method of choice in the management of this type of fistula.

COMPLICATIONS AND IMMEDIATE DANGERS

Complications of a spontaneous internal biliary fistula are few in number, the first being due to the erosion of a stone into the gastro-intestinal tract and resultant intestinal obstruction, and the second being due to an erosion of a blood vessel, with ensuing hemorrhage. The obstruction may be anywhere from the duodenum to the ileocecal valve, the ileocecal valve and region being the site of predilection.

CASE HISTORIES

A L., a 65-year-old white woman was admitted to the hospital on February 12, 1947, complaining of dysphagia, loss of appetite and right-sided abdominal pain of six months' duration. During that time she had lost 30 pounds. The patient had been constipated for years. She was at this time under the care of an internist for coronary artery disease. The rest of the history is noncontributory.

SPONTANEOUS INTERNAL BILIARY FISTULA

Physical Examination The patient was a well-developed, well-nourished, white female, who was apparently not acutely ill. The skin was sallow. The head and neck were normal. Respiratory movements were rapid and shallow. Crepitant rales were heard over both lung fields posteriorly. The blood pressure was 142/68 mm Hg. The heart borders were enlarged to the left and downward. There was an irregularity in rate and a coarse systolic murmur at the apex transmitted to the base. The abdomen was slightly rounded and the liver was palpable three fingerbreadths below the costal margin. There was some tenderness in the right upper quadrant. The rest of the physical examination was negative.

Laboratory Findings The urine on admission was negative except for a trace of albumen. Examination of the blood showed hemoglobin 81.2 per cent, or 12.6 grams,

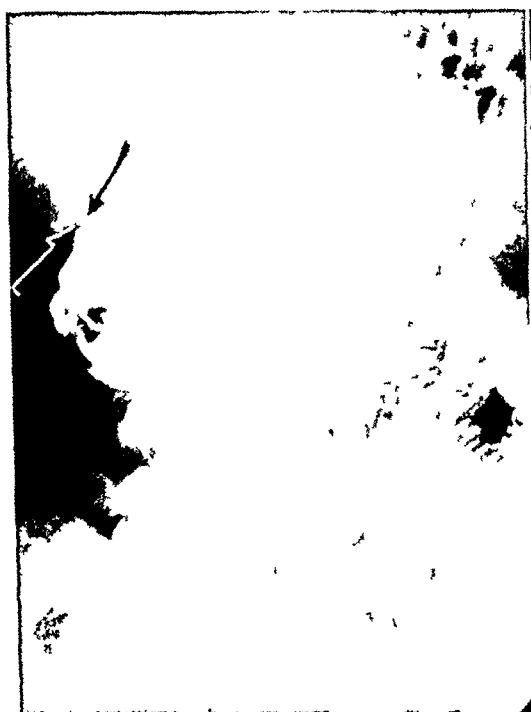


FIG 1



FIG 2

FIG 1—Photograph of a roentgenogram showing barium in the stomach, duodenum, fistulous tract (surrounded by arrows) and gallbladder. Case 1.

FIG 2—Photograph of a roentgenogram showing barium in stomach, duodenum and fistulous tract (surrounded by arrows). The gallbladder contains gas and barium. Case 2.

4.3 million red blood cells, 10,000 white blood cells. Lymphocytes 23 per cent, neutrophils 72 per cent, eosinophils 3 per cent and basophils 1 per cent. Blood chemistry showed a fasting blood sugar of 99 mg per cent, urea nitrogen of 17.4 mg per cent, icteric index of 12. An electrocardiogram showed a marked left-axis deviation with marked intraventricular conduction defect.

Roentgen rays showed nonvisualization of the gallbladder after administration of dye, and a normal stomach and colon. On fluoroscopy, barium was seen to pass from the anterior wall of the duodenal cap into an oblong cavity that appeared to be the neck of the gallbladder (Fig 1). The diagnosis of a fistulous tract between the gallbladder and the anterior wall of the duodenal cap was made. Because the duodenal cap showed no deformity, this was considered to be a primary disease of the gallbladder.

Course in Hospital In view of the history, physical examination and laboratory findings, it was decided that an operation should be performed as soon as the patient's cardiac condition warranted. Exploratory laparotomy 10 days after admission revealed

the stomach, kidneys and colon to be normal. Examination of the gallbladder region showed the duodenum to be bound down to the gallbladder by many fibrous adhesions. On separating the adhesions, a fistula between the dome of the gallbladder and the anterior portion of the duodenum was encountered. The fistula was then divided and the gallbladder removed. The gallbladder was walnut-sized, was very thick and contained numerous faceted stones. The defect in the duodenum was repaired by two layers of silk, the common duct was drained and the abdomen was closed in layers. The patient left the operating room in good condition. The summation of the operative findings are (1) cholecystoduodenal fistula, and (2) cholecystitis with cholelithiasis.

The patient made an uneventful recovery. She left the hospital 20 days after operation in good condition. Two months later she was admitted with an acute myocardial infarction, from which she recovered.



FIG 3—Photograph of a spot film of the fistulous tract. Case 2

A 62-year-old white female was admitted to the hospital on February 18, 1947, complaining of pain of three months' duration in the epigastrium and the right side of the abdomen. The pain was sharp in character and was constant. There was no vomiting or nausea. She had lost 20 pounds in the last three months. She was constantly bloated and "gassy."

Physical Examination The patient was a fairly well-developed, well-nourished woman who did not appear acutely ill. Her skin was somewhat tinged with yellow. Her head, neck and chest were normal. Tenderness was elicited over the epigastrium and right upper quadrant on deep palpation. The liver was palpable two fingerbreadths below the costal margin and its margin was well defined and regular. The rest of the examination was negative.

Laboratory Data The urine on admission was normal. Examination of the blood showed hemoglobin 60.6 per cent, or 9.4 Gm, 3.9 million red blood cells, 14,300 white blood cells, lymphocytes 19 per cent, neutrophils 77 per cent, monocytes 2 per cent and eosinophils 1 per cent. Blood chemistry showed a fasting blood sugar of 110 mg per cent, NPN of 39 mg per cent, urea of 16.6 mg per cent, icteric index 17, total protein 5.46 Gm per cent, serum albumin 3.59 Gm per cent and serum globulin 1.87 Gm per cent.

Roentgen rays showed a nonvisualization of the gallbladder after administration of the dye and a normal stomach and colon. There was an accumulation of gas in the gallbladder region. On fluoroscopy, barium was seen to pass from the upper part of the descending duodenum into a pouch lying anterolateral to it (Figs 2 and 3). No filling of the cystic or bile ducts was seen. The diagnosis of a fistulous tract between the gallbladder and the descending duodenum, with primary disease of the gallbladder, was made. As there was no visualization of the biliary ducts, in view of the patient's general condition, a malignancy was considered.

Course in Hospital In view of the history, physical findings and laboratory data, operation was advised. Preoperative preparation of the patient included blood transfusions, plasma, parenteral fluids and vitamins. However, before operation she began to run a septic fever with spiked temperature. On February 24, 1947, a laparotomy was performed. The liver had numerous nodules ranging from pinhead to pea size. The duodenum, gallbladder and inferior surface of the liver were drawn up into a very hard nodular mass that was thought to be malignant. A biopsy of one of the nodules was taken and the abdomen was closed. The patient left the operating room in good condition.

SPONTANEOUS INTERNAL BILIARY FISTULA

The pathologist's report was "Adenocarcinoma of the liver (primary) "

The patient's course after operation was uneventful except for the fact that her jaundice deepened. She was discharged from the hospital 10 days after operation. She expired at home two months later. No necropsy was performed.

CONCLUSIONS

The differential diagnosis of cholecystoduodenal fistula caused by erosion of a calculus and that caused by primary malignancy in the hepatobiliary system is very difficult to make. In the cases presented above, although the diagnosis of the fistulas was made preoperatively, causes were uncovered after exploration. It is our contention that, although the etiology in this type of lesion may be hinted at preoperatively, the true cause may be determined only at operation (Table I).

TABLE I—*Comparison of Cases*

Case	Age	Sex	Chief Complaint	Weight Loss and Duration of Symptoms	Operation	Pathology
1	62	F	Dysphagia, loss of appetite Right-sided abdominal pain	30 lbs in 6 mos	Cholecystectomy Closure of fistula	Chronic cholecystitis and cholecystoduodenal fistula
2	62	F	Pain in epigastrium, right side of abdomen	20 lbs in 3 mos	Laparotomy and biopsy of liver	Cholecystoduodenal fistula primary carcinoma of liver

SUMMARY

- 1 The literature on spontaneous internal biliary (cholecystoduodenal) fistula is reviewed.
- 2 Two new cases are presented, the etiology of one being a perforation by a calculus, and of the other, a primary malignancy of the liver.
- 3 The incidence of spontaneous internal biliary fistula is approximately per cent of all cases requiring biliary-tract surgery.
- 4 The incidence of primary carcinoma of the liver is 0.5 per cent of all cases.
- 5 The diagnosis of spontaneous internal biliary fistula (cholecystoduodenal) is made by finding barium and gas in the gallbladder after having found a nonvisualizing gallbladder.
- 6 Complications of cholecystoduodenal fistula are
 - (a) Cholangitis
 - (b) Hepatitis
 - (c) Intestinal obstruction
 - (d) Hemorrhage due to an erosion of a blood vessel

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EMPHYSEMATOUS ACUTE ABDOMEN AND SUBCUTANEOUS EMPHYSEMA FROM INTRARECTAL OPERATION*

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ACUTE ABDOMINAL SIGNS caused by emphysema in the subparietal peritoneum and in the mesentery of the colon and appendices epiploicae, associated with subcutaneous emphysema of the left abdominal and chest walls, following an operation from within the rectum and without perforation or solution of continuity of the peritoneum are extremely rare. A careful search of the literature fails to reveal any previous report of similar findings.

Subcutaneous emphysema has been reported many times and most commonly occurs in association with injury or disease of the chest or of the respiratory passages, fairly commonly as a complication of labor, but very rarely in association with acute phlegmonous appendicitis (Gruca³), perforated gastric or duodenal ulcers (McCorkle and Stevenson,⁷ Korach⁹), or in association with large intestinal surgery (Von Hasselbach,¹¹ Baumecker,¹² Brown and Hinton¹⁰).

CASE REPORT

G C, 38, housewife, first seen at the author's private office at Presbyterian Hospital.

Present Illness—There had been pain in the left side of the rectum, with radiation down the left thigh for one year. This occurred every few days and lasted for a few days, followed by constant, severe pain in the same location for the past six months. Pain was not associated with bowel movement. There had been bleeding occasionally with the passage of hard stools. There had been some gain in weight. About five months prior to the operation patient had two injections of oil into her hemorrhoids.

Proctologic Findings External examination revealed an old, healed fissure. Digital examination presented in the left anterior quadrant a linear, slightly tender area of induration, extending upward along the left anterior wall of the rectum for about 5 cm. It was 5 mm in diameter, was palpable per vagina and was suggestive of an anorectal fistula. Proctoscopic examination to 15 cm was essentially negative except for what seemed to be a fistulous opening at the mucocutaneous line on the left anteriorly.

Preoperative Examination Urine was normal. Blood: Red blood cells 3,500,000, hemoglobin 76 per cent, white blood cells 11,000, 74 per cent polymorphonuclears.

Operation An operation was performed at St. Clare's Hospital on February 4, 1947. *Findings* In the left anterior quadrant was an area of fibrosis, 5 mm in diameter and extending upwards for about 5 cm from the mucocutaneous line, in close proximity to the vaginal mucosa and probably reached to within 2 cm of the cul de sac. An area of ulceration at the mucocutaneous line on the left wall, about 5 mm in diameter, was suggestive of an internal opening of a fistula, although a probe could not be passed.

The area of ulceration and fibrosis were resected completely along the left wall of the anal canal and ampulla, leaving a large wound, measuring approximately 6 by 4 by 2 cm, after retraction of the surrounding tissue. Only the upper part of the internal sphincter was partly excised with the mass, and therefore good sphincter tone remained after the operation.

* Submitted for publication, March 1949.

On the second day following the rectal operation the patient complained of considerable distention, of abdominal pain and of chilliness. Her oral temperature rose to 103° , the pulse was 120 and respiration 20. There was no localized tenderness or rigidity. On the third day, both temperature and pulse continued to be elevated and the abdomen was greatly distended in spite of the passage of a large amount of flatus and some stool. The patient appeared acutely ill, with abdomen greatly distended, presenting generalized direct and rebound tenderness. Vaginal examination revealed diffuse tenderness. Emphysema extended over the left abdomen and the chest from the inguinal ligament to the midbreast and axillary regions. The blood count was red blood cells 3,460,000, hemoglobin 65; white blood cells 17,400 with 96 per cent polymorphonuclears.

A laparotomy for general peritonitis or mesenteric thrombosis was performed. As the abdomen was entered through a left midrectus incision, gas escaped from the subcutaneous space but no free air was released from the peritoneal cavity. There was gas in all of the subperitoneal tissues that could be visualized through a left-rectus incision. Gas was found in the mesentery of the sigmoid, in the descending colon and as far as the right transverse colon as well as in the omentum. There was no indication of any other pathologic condition.

Although the patient's condition was good, 500 cc of blood were given immediately after the operation. Twenty doses of penicillin, each of 100,000 units, and of streptomycin 0.4 Gm every three hours, together with sulfadiazine and bicarbonate of soda, were given until the temperature returned to normal on the third postoperative day. Her condition continued good throughout, the bowels began to move on the third day, emphysema of the abdominal and chest walls was much less on the fourth day and had disappeared on the sixth day. The sutures were removed and the patient was out of bed on the fifth day and was discharged in excellent condition on the sixth day after the laparotomy.

The pathologic report was that of a foreign-body giant-cell granuloma of the rectum. The histologic features of the granuloma indicated the presence of an oily or lipoidal substance which was undergoing phagocytosis.

Follow-up Two years after the laparotomy the patient's general condition was excellent and she has had no recurrence of the rectal pain.

Experimental Evidence of Subcutaneous Emphysema * The appearance of subcutaneous emphysema following intrarectal excision of a fistula was so rare that an attempt was made to reproduce this phenomenon by the injection of air alongside the rectum in two dogs.

In each animal a No. 20 needle, 2 inches long, was introduced to the left of the anus and passed upward just lateral to the rectal wall, stopping just short of the lowermost portion of the peritoneal cavity.

In dog No. 1 the air shortly appeared in the subcutaneous space of the left groin and quickly extended into the inner surface of the left thigh. Injection of 1,000 cc of air greatly increased this swelling. There was no indication of intraperitoneal or subperitoneal air. The next day the subcutaneous emphysema appeared over the entire animal as far forward as the front legs. This gradually disappeared in two weeks.

In dog No. 2, 1,000 cc of air were injected similarly alongside the rectum and quickly produced signs of peritoneal irritation. The animal's respirations were rapid and labored and the abdomen was slightly distended. One and one-half hours later the abdomen was entered through a midrectus incision. No air was encountered in the layers of the abdominal wall and none was free in the peritoneal cavity. There was however a great deal of subperitoneal air in the pelvis, and up along the posterior subperitoneal space, and in the mesentery of the colon up to the splenic flexure. Subserosal vesicles were present over the entire rectum and colon up to the splenic flexure similar to those

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observed by Nitch and Shottock⁴ in the small intestine. This animal developed signs of peritonitis, such as subperitoneal air might produce. After four days he recovered.

The appearance of subcutaneous air in one animal and subperitoneal in another fails to explain the mechanism by which subcutaneous emphysema results from intrarectal operations.

DISCUSSION

Gas-producing organisms, as in appendiceal abscess or other intestinal or abdominal-wall infections, may produce subcutaneous or subperitoneal emphysema, which is much more serious and more often fatal than when the intestinal gas diffuses through the tissues. These patients, who are very toxic from the effect of the gas-producing organisms, do not react promptly to the therapy instituted in the case presented here, but show immediate improvement and recovery following laparotomy and palliative treatment.

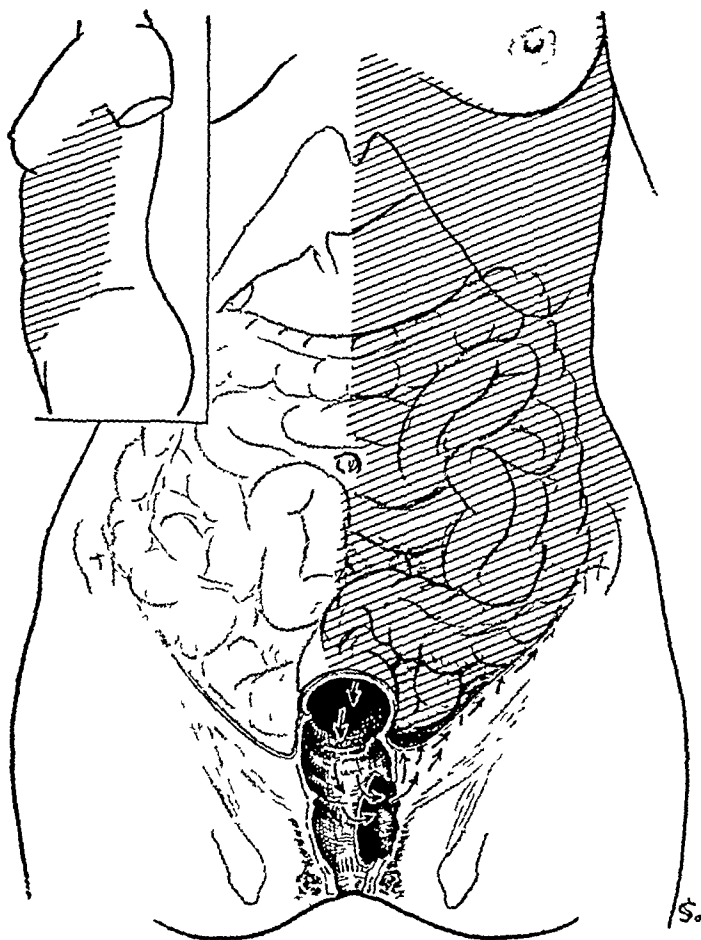


FIG 1—Showing the route of escape of gas from the intestinal lumen through the rectal wound from the fistula excision into the subperitoneal tissues of the pelvis, with diffusion into the mesentery of the colon and into the subcutaneous spaces of the left abdomen and chest.

The gas in the tissues might have come from the lumen of the markedly distended intestinal tract or it could have been manufactured by the *E. coli* or a greatly attenuated *B. aerogenes*.

It seems rather clear in retrospect that the diffusion of gas from the intestinal lumen took place through the rectal wound (Fig 1) up through the cellular tissues along the left rectovaginal septum or along the left retrorectal tissues to the mesentery of the pelvic colon, the sigmoid, the descending and transverse colon and into the subparietal peritoneum.

as a result of the greater gas pressure in the intestinal lumen. It is possible that diffusion of the gas took place from the subparietal space through the fascial and muscular layers of the abdominal wall above Poupart's ligament to the subcutaneous spaces of the abdomen and chest up to the left midbreast region. It is believed more likely, however, that the subperitoneal gas diffused through the thinned-out fascia in the region of the symphysis to the subcutaneous region, where it could have spread to any part of this space.

SUMMARY

The first operation consisted in the removal of a mass of tissue, including the mucosa and a complete thickness of the smooth muscles of the rectal wall in the right anterior quadrant adjacent to the vaginal wall, extending up very close to the pelvic peritoneum. The appearance of the marked abdominal distention was followed in from 18 to 24 hours by external emphysema of the left abdominal and chest walls, extending from Poupart's ligament to the midbreast region.

The patient was acutely ill for 24 hours preceding laparotomy, the oral temperature was 103°, the pulse 120, with direct and rebound tenderness, and an elevated blood count. Therefore, an element of infection was predicated and a simple exploratory laparotomy was done three days after the rectal operation. Rectal wound culture immediately following laparotomy showed pure *E. coli*. Prompt and complete recovery followed simple laparotomy and chemotherapy.

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BILATERAL BROAD LIGAMENT LIPOMATA

REPORT OF A CASE AND REVIEW OF THE LITERATURE¹

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BROAD-LIGAMENT LIPOMATA are rare lesions, and to date only 19 cases have been reported in 14 articles^{2, 3, 5, 6, 8, 11, 13, 18}

The first case was reported by Pollock in 1852¹⁵. However, the rarity of this condition is probably more apparent than real, since several^{7, 10} have mentioned but not actually reported their cases.

The origin of fatty tissue in the broad ligament, normally devoid of such tissue, poses a problem. Metaplasia of connective tissue has been suggested.⁷ Growth downward from retroperitoneal tumor higher in the abdominal cavity may occur. Lockyer¹⁰ discards two cases of so-called broad-ligament lipomata that presumably originated from rupture of dermoid cysts.^{1, 4}

The symptomatology, as recorded, is scanty. The patients' ages range from 31 to 70 years. Of the cases in which the age was recorded six were in the fourth, six in the sixth (including ours) and one each was in the fifth and the eighth decades. In two cases (of five reported by Flickinger and Masson)⁶ the tumors presented in the perineal region. Preoperatively, parovarian cyst,¹⁷ tuberculous peritonitis¹⁶ and hydrosalpinx⁸ were considered likely diagnoses. In one case a preoperative diagnosis of incomplete abortion was justified.⁸ In only two cases, including our own, was the correct condition of a parovarian tumor suspected before operation.⁶

Associated pathology consisted of dermoid cysts,^{3, 10} fibromyomata uteri,⁷ chronic salpingitis⁶ and in two cases adenocarcinoma of the endometrium.^{6, 17} In one instance the lipoma was large enough, presumably, to cause dilatation of the corresponding ureter.¹⁰

The lipomata listed vary greatly in size and location. Grossly, they may be as small as 9 mm. or as large as 90 cm. in diameter.¹¹ Lobulation may be present.⁸ Occasionally, they may occur as small growths in the mesosalpinx.¹⁷ In one case the tumor dissected alongside the vaginal canal to present in the perineum, in another, the tumor herniated through the obturator foramen.⁶ The recorded lipomata were right-sided in eight cases, left-sided in four, bilateral in three (ours makes the fourth) and unrecorded in four.

Of those examined histologically all were reported as lipomata except one which, microscopically, was a fibromyxolipoma.⁶ The tumors are benign, curable by simple excision. If large enough, the lipoma may be intimately associated with deep pelvic vessels⁸ and may be removed with difficulty. Recur-

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rence has been reported once.⁶ Retroperitoneal lipomata above the pelvic brim however, tend to both recurrence and malignant change.¹²

The following is a case report of a 58-year-old white woman who had symptomless bilateral broad-ligament lipomata discovered on routine pelvic examination and diagnosed preoperatively as parovarian cysts.

CASE REPORT

Mrs. M. H., age 58 years, gravida 4, para 4, weight 186 pounds, first consulted Dr. Lewis C. Scheffey at Jefferson Medical College Hospital in June, 1946, for an opinion as to whether or not an advised operation for "ovarian cysts" was indicated.

The patient's menopause had occurred in 1939. Since then there had been no post-menopausal bleeding or discharge. Her only complaint was occasional mild backache. Aside from a history of high blood pressure, her past history was negative. She had had no previous operations.

General physical examination was essentially negative except for obesity and a blood pressure of 184/94. Pelvic examination disclosed a multiparous introitus, slight relaxation of the anterior and posterior vaginal walls. The cervix was intact with a small cervical polyp. The uterine body seemed to be of normal size, anteflexed and anteverted. Each adnexal area, however, contained a fixed semicystic enlargement about the size of an orange, the left-sided enlargement being somewhat larger than the one on the right. A tentative diagnosis of probable bilateral parovarian, possibly ovarian, cysts, was made.

In the absence of symptoms, an expectant policy was decided upon. The patient was rechecked both systemically and gynecologically every few months. In the latter part of March, 1947, however, the left-sided enlargement seemed to be increasing in dimensions and on that basis laparotomy was advised and accepted.

On the patient's admission to the hospital, preoperative studies disclosed a normal blood count and urinalysis, a urea clearance of 65 per cent average normal. The sedimentation rate was 22 mm in one hour, 27 mm in two hours.

The patient was operated upon by Doctor Scheffey, May 20, 1947. After routine vaginal antisepsis, curettage was performed. No curettings were obtained. Cervical polypectomy was followed by endothermic cervical resection. The abdomen was prepared with iodine and alcohol and the pelvic organs exposed through a right paramedian incision. The uterus, tubes and ovaries were atrophic, presenting no gross abnormalities. The appendix was uninflamed but elongated with a very fatty meso-appendix. Of most interest were bilateral broad-ligament enlargements (each about 8 cm in diameter) adjacent to the round ligaments and inguinal canals. These were found to be of fatty tissue. The lipomata were extirpated by blunt dissection, the areas of removal peritonealized. A routine appendectomy was carried out. The abdomen was closed in layers.

Pathologic Report. The cervical polyp was histologically benign, and the appendix was normal. The bilateral broad-ligament masses were globular pieces of tissue, varying from 3 to 5 cm in diameter, the stroma was composed of homogenous, yellowish soft glistening, adipose tissue. Microscopically, the stroma was made up of typical acellular adipose tissue, throughout which there were several collections of normal-appearing lymphocytes. *Diagnosis.* Lipomas.

The patient had a normal convalescence and was discharged from the hospital on the eleventh postoperative day. At this writing (February, 1949) she continues to do well with no pelvic complaints and with normal pelvic findings.

SUMMARY

A brief survey of recorded broad-ligament lipomata is made. They are unusual benign lesions bilateral in one-fifth (4 out of 20) of the recorded cases. They vary from the size of a bean to that of an adult head. Exact preoperative

BILATERAL BROAD LIGAMENT LIPOMATA

diagnosis is, of course, very difficult, surgical investigation being the only means of eliminating more serious conditions. Two (10 per cent) of the recorded cases of broad-ligament lipomata were associated with corpus carcinoma.

A case report of a 58-year-old, postmenopausal white woman with symptomless bilateral broad-ligament lipomata, without recurrence more than a year postoperatively, is presented.

Note The authors wish to thank Dr Lewis C Scheffey, Professor of Obstetrics and Gynecology, Head of the Department and Director of the Division of Gynecology, for his interest and encouragement in the preparation of this review.

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Editorial . . .

GENERAL SURGICAL TRAINING AND THE SPECIALTIES

A CENTURY AGO when our population was only a fraction of what it is today, surgeons were few. The internist was often the man who performed the lifesaving operation, for not many men limited their practice to the narrow field of surgery as it was then. Specialists as we know them today were practically nonexistent. But through the years the ratio of surgeons to the population has increased, and surgery has widened its scope with greater safety to the patient. Decade after decade has shown a rapid increase in the number of well trained surgeons and great expansion in their fields of activity. Once, all surgical practice was almost entirely in the hands of the general surgeon, but its scope is now so vast that no one man would profess to be proficient in all its branches.

Since the turn of the century, many of the ablest surgeons have limited themselves to special parts of the body, and by close application and exhaustive research have extended the frontiers of surgery in their elected fields to create the surgical specialties of today.

The first branches of surgery to take their places as specialties were ophthalmology, otolaryngology, gynecology, and orthopedics. More recently, urology, neurosurgery, and plastic surgery have attracted men to specialization. Complete segregation of ophthalmology and otolaryngology was readily accomplished, for the general surgeon was glad to relinquish this part of the body to those whose interest lay in this field. In the other specialties there is an overlap with general surgery which makes it more difficult to draw a firm line of distinction. But the tendency to create special fields of surgery continues. Lately, it has been proposed to recognize thoracic surgery as a specialty, and to make proctology and gastroenterology joint activities of medicine and surgery, divorced from general surgery. This trend could lead to an ultimate breakdown of surgery into multiple specialties, each treating its separate portion of the body. Were the human organism simply an aggregate of mechanical parts like an automobile this might be an acceptable policy, but it is obviously not the case.

Our population now approaches 145,000,000, from which at least 20,000 medical school graduates have entered surgery. Each year new avenues to surgical therapy are opened, but at the same time the old, established approaches are not closed by the advent of such medical discoveries as chemotherapy. Surgery is still necessary and the volume of work to be done is great. At the present time, under optimum circumstances, surgery provides an unprecedented opportunity to allay human suffering from injury, deformity

and disease. It is undertaken with ever-decreasing morbidity and mortality, a sign of the rapid progress which has been made in the diagnosis of surgical conditions and in surgical technic and care.

To cover the variety of surgical endeavor with the special abilities and widely different interests of individual surgeons, it might seem wise to continue the formation of specialties, and the university hospitals with their medical schools together with the large clinics, so abundant in material, have fostered such a breakdown for surgery and medicine. But though the development of new surgical specialties over the past thirty years has been justified by the work accomplished, it has led to a tendency for further subdivision that is narrowly based on either anatomical regions, such as the head, neck or extremities, or on the systems, cardiovascular, nervous, gastroenterological and urological. The fact that surgery was extended by specialization is not an indication that further breakdown will produce greater progress. The men who originally developed the specialties were, without exception, well grounded in general surgery. If basic surgical training is lacking, a specialist is likely to see only the conditions related to his particular field of interest, rather than evaluate the patient as a whole.

Many advances in surgical therapy have resulted from the investigation and development of new methods by men who devoted themselves to a limited field of surgery. Some regions of the body, once neglected because they were considered unapproachable, have been transformed into fields of highly successful accomplishment through the work of small groups of surgeons concentrating all their energy on the solution of seemingly hopeless problems. Neurosurgery is an outstanding example of such effort. Prior to the time of Harvey Cushing's unceasing studies and experiments, the mortality rate associated with the removal of brain tumors was over 50 per cent, and the majority of the lesions were not diagnosed before death. By the close of his active career he had reduced the mortality rate for these cases to 5 per cent, and even more important, he had opened up a new diagnostic approach which brought to light certain clinical entities until then unrecognized.

The present trend towards over-specialization is unfortunate, because more and more young men are seeking training in the specialties without first completing their full basic training in general surgery. If American surgery is to continue on the high plane established over the past century, and if it is to contribute further improvement to patient care, then it is important that we consider critically the fundamental training a surgeon should receive. The basic principles of surgery apply to every specialty, and training in general surgery provides the best foundation for evaluating a patient's condition without undue emphasis on the part of the human anatomy that is the specialist's chief interest. If the specialties are manned by men with general training who therefore think of a patient as a complete individual, they will be far better equipped to give the best in surgical therapy.

Specialists tend to sponsor specialty hospitals. The preceding two genera-

tions saw many such hospitals established throughout the country. More recently, however, there has been a trend to reaffiliate these institutions with the large general hospitals and medical centers. The specialty hospital, like the specialty, may make great contributions, since it serves as a place to concentrate the clinical material and talent so essential for advancement. At present there is renewed interest in cancer and in cardiovascular disease, and both, because they account for so high a proportion of the deaths in our population, properly merit special consideration by the people's money and by the profession's thought and effort. The objectives behind an institution for improving the diagnosis and treatment of cancer are important and praiseworthy, but how they are carried out should depend on the country's needs. Whether such a hospital should produce cancer specialists rather than further train those general surgeons who are especially interested in cancer is a debatable question. It is my opinion that the country at large needs the latter, namely, able surgeons who are trained in the best treatment for cancer, rather than "cancer specialists" trained only in cancer work.

To increase the number of specialties and reduce the requirements in general surgery training would prove a pitfall to American surgery. There can be little justification, in my opinion, for establishing a specialty such as proctology, which has been sponsored with little emphasis on general surgery training, but is designed to teach "medical and surgical proctology." Such a designation would lead the public to believe that a man who has undergone this training would be the best equipped to treat rectal conditions. It is obvious that the patient with a carcinoma of the rectum is safest in the hands of an able general surgeon who has technical skill and judgment of the highest order; he should not be victimized by those who can give him only palliative treatment because they lack the training which would enable them to undertake major surgical procedures.

The American Board of Surgery is to be commended for establishing standards of qualification for those who wish to do general surgery. It has also stimulated the desire to provide more adequate training facilities. This goal is sought by all specialty boards, and their aim is likewise commendable but unfortunately there is a trend at present among these boards to minimize the requirements in general surgical training for certification in a specialty. The best in surgical accomplishment, no matter what the field, depends fundamentally on these principles of basic training: that a surgeon is first of all well aware that each part of the human body is related to all other parts; second, that a disturbance to one organ will affect the body as a whole; and finally, that relatively difficult procedures require more than particular knowledge of a special part of the body—that they demand full understanding of the basic principles of general surgery.

Is the trend to establish more and more specialties an indication of deterioration in American surgery? We should keep clearly in mind that to divide general surgery into narrower specialties has nothing of merit in itself. To

achieve the goal of the best in surgical therapy various approaches will be tried, but the general aim should not be obliterated by innovations that deal chiefly with organization and divide responsibility in caring for the patient. These are likely to emphasize the specialty rather than the fundamental principles of surgery that are so basically important.

FRANK GLENN

EDITORIAL ADDRESS

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BOOK REVIEW

SHOCK AND ALLIED FORMS OF FAILURE OF THE CIRCULATION, by H. H. Davis, New York, Grune and Stratton, 1949

This book is essentially a huge collective review of the literature on shock and as such, it is very well done. It is carefully and completely documented in a tremendous bibliography. If the reader is interested in research in the field of shock and shock therapy, he will find this to be a good source book. The practitioner will find the index very useful in checking information limited to specific problems arising in practice. In contrast to the post-graduate student of the subject, one would hesitate to recommend such a work to a medical student because he would, in all probability, become lost in the maze of controversial literature and minutiae and carry away with him no clear-cut ideas to apply to his clinical problems.

Our ignorance of how to treat shock is emphasized by the fact that although the author devotes 516 pages to describing the physiological and biochemical aspects of the shock state, he needs only 59 pages to do justice to the matter of treatment.

This reviewer disapproves of the term "pseudoirreversible shock" proposed by the author. As used by him, it includes simply incompletely treated cases of shock and therefore seems to serve no useful purpose.

The final chapter, which is on treatment, contains a few statements with which many will take issue. Some of these concern the use of plasma in burn shock and the categorical rule given for governing rate of transfusion in shock. Very little is said about ante operative blood volume studies or the measurement of venous pressure during massive transfusion.

MILTON R. PORTER, M.D.

BOOKS RECEIVED

CHARLES L. BURSTEIN

Fundamental Considerations in Anesthesia The Macmillan Company, New York, 1949

RICHARD H. OVERHOLD
LAZARO LANGER

The Technique of Pulmonary Resection Charles C. Thomas, Springfield, Illinois, 1949

GEORGE R. MOON

How to Become a Doctor The Blakiston Company Philadelphia, Pennsylvania, 1949

PEARL LEWIS

Eating for Health The Macmillan Company, New York, New York, 1948

HARRY E. BACON

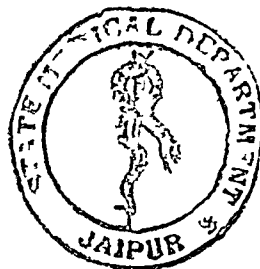
Anus—Rectum—Sigmoid Colon: Diagnosis and Treatment Volumes I and II, Third Edition J. B. Lippincott Company, Philadelphia, Pennsylvania 1949

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MEETING HELD AT ST LOUIS, MO , APRIL 20, 21, 22, 1949

ADDRESS OF THE PRESIDENT

MISSION ACCOMPLISHED THE TASK AHEAD*

FRED W RANKIN, M D

LEXINGTON, KENTUCKY

IT IS MY FIRST and very agreeable duty to express to you my profound appreciation of the honor of my selection to preside over your deliberations at this, the sixty-ninth annual meeting. This accolade of surgery comes to me, I am fully conscious, not because of any personal achievement or any merit which I might possess, but as a recognition bestowed upon a representative of the surgeons of the United States who served in the armed forces during World War II.

Like many other members of this Association, I have been privileged to serve in the Army of the United States during two world wars. Because of that dual experience it is meet that I address you on the activities of the Medical Department of the Army during World War II, that I acknowledge my indebtedness to the men who helped me carry out my duties, and that, in particular, I discuss the immediate care and rehabilitation of battle casualties. All phases of their medical management were deeply and favorably influenced by the counsel and aid of almost every member of this Association, whether or not he served in uniform.

* Read before the American Surgical Association, St Louis, Mo , April 20, 1949

We still live in a twilight zone of tension. The world still wears the habiliments of war. The guns may be silent, but there is still no peace. Conflicting ideologies, endless irritations, unfettered national ambitions and world-wide selfishness all seem to be driving inevitably toward World War III. We still do not know whether or not there will be peace in our time. Until we know, and know beyond peradventure, we have no alternative but military preparedness, of which medical preparedness is an essential part.

THE MEDICAL PROFESSION IN THE TWO WORLD WARS

The long shadow of World War II fell across the United States long before we became active participants in it. Yet we found ourselves plunged into it with the abruptness which has characterized our entrance into most of the wars of our history. And, as has happened in other wars, the armed forces in general and the Medical Departments of the Army and Navy in particular were gravely unprepared. The explanation, of course, is simple. This is a free and democratic country, where many factors militate against preparedness and where the will of the people does not countenance, indeed is actually hostile to, a large military establishment.

Probably the most important reason, from the medical standpoint, of our perpetual unreadiness for war is that when war comes, civilian physicians must bear the entire burden of the professional services.

At the outbreak of hostilities on 7 December, 1941, there were approximately 1,200 medical officers in the Regular Army Medical Corps. Some Reserve and National Guard officers were already serving in the army that was coming into being under the Selective Service Act, but with the rapid expansion required when we entered the war more vigorous action was demanded. It was necessary, without further delay, to mobilize all physicians in these categories who were not already in service, to equip, train and allocate them, and to institute, in conjunction with other governmental agencies, procedures which would meet the future needs of the services. In World War I some 31,000 medical officers were commissioned from civilian life. Before World War II ended, approximately 60,000 medical officers had been commissioned in the Army and the Air Force and approximately 12,000 had been commissioned in the Navy. As these figures show, the response of the American medical profession to the needs of the nation was prompt and wholehearted. It recognized the task which had been placed upon it by our active participation in the war, accepted its new responsibilities, and began to reorganize the whole pattern of its professional life. One thing that it promptly perceived was that protection of the civilian health was just as large and important a problem as was the supply to the armed forces of an adequate number of medical officers to care for the sick and wounded. The dual performance was competently achieved, albeit with some of the wasteful excesses characteristic of all previous wars.

At the outbreak of World War I, as Brewer pointed out in his presidential

address before this Association in 1920, 153 of its members, 33 of whom were Senior Fellows, volunteered for service and served in the armed forces at home, in the American Expeditionary Force in France, or in other wartime activities of the government. During World War II, when the over-all situation was so greatly changed, the response of the Association to the needs of the nation was equally praiseworthy. Fifty-eight of the membership, including six Senior Fellows, were in uniform, and practically all of the remaining members were engaged, either directly or indirectly, in some phase of military activity in medical schools and on Selective Service Boards or were participating in the war effort in some advisory capacity.

I would be remiss in my duty did I not acknowledge the debt of the Army Medical Corps to a special group of medical men, practically all of them members of this Association, the Committee on Surgery of the Division of Medical Sciences of the National Research Council. From the professional standpoint their untiring efforts and mature advice contributed inestimably to the conduct of the war. They evaluated innumerable scientific avenues of approach to medicomilitary problems, including, among others, the control of infection, the evaluation of blood and blood substitutes, the influences of various agents and processes on wound healing, the efficacy—or the lack thereof—of many methods of wound sterilization, and the value of protective armor. In addition to these specific accomplishments, and perhaps just as important, this committee stood as a stout buffer against all adventurers, the well-meaning and the fraudulent alike, who offered to the government in overwhelming numbers gadgets of various kinds and therapeutic cure-alls.

The work of this committee on the proper evaluation of agents to control infection is a service of which I would speak particularly. At the outbreak of the war the Surgeon General was placed in a real dilemma concerning the use of chemotherapeutic agents.

He received confusing advice from certain nonsurgical specialists—overly-enthusiastic—who arrogated to themselves the treatment of infections previously regarded as entirely in the province of the surgeon. His difficulty was compounded by reports, later proved to be overly-enthusiastic, concerning the efficacy of the sulfonamides at the Pearl Harbor disaster. As a result, grave mistakes were made early in the war. Later the situation was clarified, the intensive scientific studies of the Committee on Surgery and of its Subcommittee on Surgical Infections done in civilian hospitals furnishing the solid background for the military experience by which bacteriocidal and bacteriostatic drugs were relegated to their proper status, that is, adjuncts to adequate surgery.

In numerous respects a comparison of the medical aspects of World War I and World War II is instructive. American participation in World War I was short and was confined to a single theater, the European. In World War II, it extended over almost four of the six years of the conflict and four major theaters of operations were developed medically as well as militarily.

In World War I the war on the European front was static and trench warfare was the rule. Troops therefore lived underground amid unbelievably bad hygienic conditions, lack of sanitation, and exposure to disease, which probably caused more casualties than did enemy weapons. Their physical condition degenerated and recovery from wounds and infections was slow.

In World War II the advent of armored vehicles which operated in the open made for mobility on practically every front, though the disappearance of trench warfare did not prevent a tragic experience with trench foot. American troops landed in Africa, Italy, Normandy and France, and on innumerable islands in the Pacific. For the most part they were not battle-ried, but they were physically fit and they had been acclimatized to active service conditions. Along with the activity on the fighting fronts came an enormously increased fire power *on the ground, through the air, and by mechanized units*, a combination of circumstances which required innovations in the care of the wounded.

THE CONSULTANT SYSTEM IN WORLD WAR II

Within six weeks after the United States had entered World War II there was established in the Office of the Surgeon General a professional services division which was in sharp contrast to the prototype of this organization as it operated in World War I. In that war the consultants' division consisted of a casual group of medical men who served only part-time and who, in many instances, were not even in uniform. These civilian surgeons, many of them the most eminent in the country, were invited to the Office of the Surgeon General to advise him, sometimes on a rotating basis, sometimes merely as the needs arose, but all of them maintained their civilian responsibilities. In World War II, I think it is greatly to the credit of Surgeon Generals Magee and Kirk that the consultants in their office served in uniform throughout the war, on the sound basic concept that medicine and surgery should be practiced on a parallel to that in civilian life, namely, by specialization.

The heart of the professional program of the Army Medical Corps was the consultant service, manned by properly trained, widely experienced, and fully equipped medical men. I think it can fairly be said that this concept was fully implemented. All consultants were selected after thoughtful consideration, on the basis of their training, ability, accomplishments and professional eminence. I need not remind you how many of them, both in the Zone of the Interior and overseas, were Fellows of this Association.

When the Professional Services Division was formed in the Office of the Surgeon General, there were three major specialties, surgery, medicine and preventive medicine, represented. Later a division of neuropsychiatry was added. Consultants in the various subspecialties were then appointed, not only in the Surgeon General's Office but also in every service command in the Zone of the Interior and in the Mediterranean, European, China-Burma-India, and Pacific theaters. Here, again, comparison with World War I

suggests itself. There was nothing like this type of organization in the service commands in this country in World War I.

In the overseas theater, however, a consultant service was developed under General J. M. T. Finney and Colonel W. L. Keller, both of them Fellows of this Association, which had the war lasted longer, would unquestionably have expanded and operated along much the same lines as the overseas consultant services in World War II.

The function of the surgical consultants in World War II may be loosely defined as the establishment and promotion of high surgical standards by (1) formulation of policies and (2) selection and allocation of personnel. The first of these objectives obviously depended upon the second. It was immediately apparent to me upon my appointment as Chief Surgical Consultant that if the care of battle casualties and the conduct of surgical procedures were to be in military hospitals in the field and in the Zone of the Interior, on the level of similar accomplishments in civilian practice the key to success lay in the selection of properly trained personnel. Constant assessment and reassessment of the assignment of surgeons before we were actually engaged in combat and throughout the war were perhaps of greater importance and more fruitful in results than most of the other duties carried out by the Surgical Consultants Division.

The highly critical comments often made concerning the malassignment of medical officers were, I am afraid, sometimes justified from the individual point of view. In an organization which within the space of a few months, had mushroomed from less than 1,300 men to 35 times that number, it was almost inevitable that some administrative errors should occur. I assure you, however, that whenever they were found, they were vigorously pursued by the Surgeon General's Office and I think that on the whole they were kept to a minimum. That considerable success was achieved in the assignment of surgical personnel is evident from a survey made in 1945. A sample of 922 surgeons qualified in various specialties and serving in the Zone of the Interior showed that 96 per cent of them were doing surgery in their own fields in Army hospitals. The other 37 were serving as consultants in the nine service commands or were assigned to the Surgeon General's Office.

It was the earnest desire and consistent endeavor of the theater and Army consultants that there be a parallel disposition of specialized talent in overseas installations, and it can fairly be said that considerable success was achieved. The program of supervision, co-ordination and policy making which originated in the Surgeon General's Office and which was integrated throughout the various echelons in the Zone of the Interior and theaters of operations resulted in a remarkably equable disposition of talent and in the consequent maintenance of a standard of surgery that was always comparable, and frequently superior, to that available to a cross section of the civilian population.

The consultant system was the keystone of the arch, the essential element, of the laudable surgical record achieved by the Army Medical Corps in World

War II I tell you nothing, however, that you do not already know when I say to you that numerous organizational difficulties attended its full implementation. For this, there were a variety of reasons—so-called bulk allotment of personnel, limitations of rank, rigidity of unit organization, and the absence of a consultant specification in Tables of Organization. Furthermore, the line of communication within the consultant system, itself, was extremely unsatisfactory. Since the consultants were essentially advisors, without command responsibilities, they should have had what they never had, a clear line of communication within their own system, organizationally pyramidal in structure and converging at the summit in the person of the chief consultant. Within such a system, had it existed, technical control could have flowed down peripherally, flexibility of movement would have been possible, coordination of activity would have been encouraged, exchange of information would have been prompted, and the whole system of operation would have been more effective.

The relationship of the consulting surgeon to an army or a theater or a service-command necessarily revolved around his relations with the line. A medical officer, regardless of his rank, always had to keep in mind the important fact that he was an advisor and had to remain an advisor. His opinions, properly, had to be subordinated to the tactical situation. Yet despite these restrictions it was his duty to express his opinion firmly, fearlessly and tactfully. It was his duty to raise his voice although none knew better than he that all too often, like the Prophet of Israel, his was a "voice crying in the wilderness." His opinions on important and frequently vital professional subjects were usually accepted, were occasionally rejected, and were almost always modified. Frustration, in short, was likely to be the lot of a medical officer, regardless of the echelon in which he served.

THE CONSULTANT SYSTEM IN OVERSEAS THEATERS OF OPERATION

Let us examine, for a moment, the work of the consultant system in overseas theaters of operations in World War II. In the Pacific Theater the consultant system came into being late and was never fully implemented, partly because of the shortage of personnel and partly because of the deliberate postponement of a major effort in that area until the conclusion of the European phase of the war.

In the Mediterranean Theater, which served somewhat as a proving ground for future medical activities, the operation was confined to, and was executed by, a single army, the Fifth, whose maximum strength was eight American divisions. The operation was both holding and assault in character. The medical personnel was probably the best ever supplied to an army operating in the field. The professional care of battle casualties was excellent.

The European Theater of Operation was recognized by one and all as the major theater of the war. The fighting was primarily offensive. The more than 70 American divisions, together with the numerous Allied divisions which

participated in the assault, were held together in Army Groups instead of single armies. In this theater the care of the wounded was handled admirably due in large measure to the indomitable spirit and remarkable personality of the late General Elliott C. Cutler. The liaison which he established with the American Command and with British and French surgeons was unusually happy. The result of his efforts was the surpassingly good care which our battle casualties received.

The successes of the consultant system in the major theaters of operations, as well as in the Zone of the Interior, were personal triumphs for the consultants. They refused to be shackled by the circumstances under which they had to work, and the outcome was happy and desirable. We would do well to remember, however, that had they been men of different personalities, men of less professional and moral courage, the outcome might well have been different and the medical care of battle casualties might well have been seriously handicapped.

All surgical consultants in overseas theaters functioned with extreme effectiveness, but they had to rise above the system to do it. They had to overcome the limitations of authority and the difficulties introduced by the subordination of the Army Medical Corps, a professional service to a Service of Supply which dealt in commodities and in nonprofessional services.

SPECIALIZATION IN THE Z I

The administration of the surgical specialties in the Zone of the Interior differed from their administration in zones of combat only in the number of personnel employed under changing conditions. I acknowledge my obligation to the consultants who worked in the United States during the war. They carried out manifold duties and bore heavy responsibilities. If, however, I were asked to name their greatest achievement I would say, without hesitation, that it was the establishment of specialized surgical centers in the general hospitals. These centers, which clearly reflected the Surgeon General's desire to foster specialized surgical care, represented an innovation in the professional services of the Army.

As time passed, there were created six amputation centers, 21 neurosurgical centers, five thoracic surgery centers, three vascular surgery centers, eight plastic surgery centers, eight centers for ophthalmologic surgery, two centers for the rehabilitation of the blind, and three centers for the rehabilitation of the deaf. These installations were provided with the most modern general and specialized technical equipment required in each field. More important, they were staffed by men who were highly competent in their specialties and whose time and effort could be used to the fullest advantage, and with a minimum of waste, because their patients were concentrated. I do not exaggerate when I say that many casualties, who in earlier wars would have remained casualties forever, were restored to useful and productive lives.

These centers served a further purpose. They afforded an opportunity for on-the-job training to young surgeons whose residencies and apprenticeships had been interrupted by the war. For obvious reasons, nothing approaching the complete training afforded by civilian teaching hospitals in peacetime could be undertaken in these centers, if only because the pressure of work would not permit it. But it is not too much to say that the training program which was carried out under civilian specialists in uniform compared very favorably with its counterpart in civilian practice. The specialty boards accepted that point of view when they decided to grant credits for it in their requirements for certification.

The training program in neurosurgery is perhaps the best illustration of this achievement. It was undertaken as a matter of sheer necessity. When, in February, 1942, we began to mobilize specialized talent for the care of our armies overseas and at home we were astounded to discover that in the whole United States there were only 154 certified neurosurgeons. The significance of that number did not become fully apparent, however, until we found that to meet the Tables of Organization of Army hospitals it would be necessary to strip every civilian clinic of its neurosurgical personnel. And even then the Army would have been left short.

Army needs had to be met. Something has to be left for civilian needs. The most practical solution was to train young general surgeons, as quickly as possible, in the essentials of neurosurgery. A program of instruction was therefore set up, the first part consisting of didactic lectures and anatomic dissections, the second part of clinical training in neurosurgical centers in the United States. In these centers, by lectures, ward rounds, work in the operating theater, and ward work, the young surgeons who had completed their didactic and theoretical training were taught the practical aspects of traumatic neurosurgery. In all, some 200 young general surgeons were thus trained, and the exceptionally fine service which they rendered overseas and at home is the background for the unprecedentedly good care which neurosurgical casualties received in World War II. Without this training program it could not possibly have been accomplished.

To my mind, this demonstration of the possibility of rapid training of specialists in an emergency is one of the major medical accomplishments of World War II. If it proved applicable to the training of neurosurgeons in time of war, it should be equally applicable to the training of other surgical specialists in any other emergency. That is a significant possibility from the military point of view, but it has its lessons for civilians as well. In the pre-war years there was a decided tendency in all the surgical specialties, including neurosurgery, to underestimate, and even to belittle, the value of a sound background in general surgery. The war experience makes it possible to say flatly that this sort of background is highly important in the training of all surgical specialists, and that in time of war the possession of such a background is almost essential.

THE CLINICAL ACCOMPLISHMENTS OF WORLD WAR II

Mortality In each major war for which statistics are available, beginning with the Peninsular Wars, the death rate of the preceding war has been halved. The improvement in World War II was even greater, the percentage of men dying of wounds being 33, as compared with 81 in World War I. In wounds of the most potentially lethal portions of the body, that is, the head, chest and abdomen, the mortality rates in World War II were almost 65 per cent lower than similar rates in World War I. This is a gain that is worthy of high praise, though the unhappy realization remains that had we learned many of our lessons earlier in World War II, we might have saved many more lives. I make that statement soberly, with full consciousness that World War II lasted much longer than World War I, that it was fought over different types of terrain, and that it was fought with far more lethal weapons.

The four factors which most vitally influenced the mortality and morbidity rates for battle injuries in World War II were

- 1 The availability of a large number of excellently trained young surgeons, who could be placed well forward in combat areas

- 2 Improved methods of resuscitation, including, among other things, the lavish use of blood and blood plasma. This improvement underlay success in all fields of surgery in World War II, and it would be impossible to speak of it without making special mention of Colonel Henry K. Beecher. To him goes the credit for the pattern of resuscitation developed in the Fifth Army and advantageously followed throughout the rest of the war by all other Army elements. His concept of resuscitation and its able implementation resulted in delivering to the surgeon a patient who, in spite of the circumstances of battle, always presented a better risk than he had presented when he was brought off the field and who frequently presented an optimum risk.

- 3 The control of infection by antibiotics and chemotherapeutic agents which, it should be emphasized once more, were properly used only as adjuncts to surgery.

- 4 Improved transportation facilities and, in particular, transportation by air, which permitted rapid evacuation from forward positions all the way to the Zone of the Interior.

Upon these factors and their ancillary ramifications rested the hopes of the surgical program. The ultimate evaluation of the care of battle casualties and the marked lowering in the general and special mortality rates amply testify to the competence with which they were applied.

The Management of Wounds It would be difficult to challenge the assertion that no epoch-making discoveries came out of World War II in respect to the treatment of battle wounds. Old principles employed in past wars were modified and surgical progress was forwarded by many ingenious innovations, but nothing really new came into existence. The three stages of wound management, namely, early and complete debridement, delayed (so-called sec-

ondary) wound closure, and reconstructive surgery, were exactly similar to the principles employed in World War I. They were modified and refined in practice, with infinite advantage to the wounded soldier, but as principles they remained unchanged.

Debridement was done close to the front line. Transportation facilities permitted rapid evacuation to hospitals far to the rear, or, in the European Theater, to England, for the second phase of the program. Practically all of the reconstructive surgery was done in hospitals in the Zone of the Interior.

The debridement of war wounds had its beginning in principle under Desault and his pupil Larrey, Napoleon's Army surgeon, who was unquestionably one of the great military surgeons of all time. The exact meaning of the term, however, has somewhat altered over the years. Desault and Larrey described debridement as a deep incision for the purpose of exposing the anatomic structures and exploring and draining the wound, but Desault believed, as the surgeons of World War II learned if they did not already know, that the excision of dead tissue was the more important part of the procedure.

Recent usage has made the term debridement synonymous with excision or revision of the wound, but there was so little difference between the principles and practice of this operation as it was performed in World War I and in World War II that Pool's article on the subject published in 1919 might equally well have been published after the second World War.

After debridement, however, the surgeons of World War II had an enormous advantage over the surgeons of World War I. In the late war there were available extraordinarily efficacious sterilizing agents which controlled infection, even of the gravest kind. Gas infection, which had been so frequent in World War I, was conspicuously infrequent in World War II, partly because of prompt operation and satisfactory transportation facilities, partly because of the more favorable terrain over which the fighting was done, and in large part because of the use of chemotherapeutic and antibiotic agents which, although they perhaps had little if any effect upon gas-producing organisms, were definitely inhibitory to symbiotic bacteria. When one recalls that sterilization of wounds in World War I was chiefly confined to the utilization of the cumbersome and inconvenient Carrel-Dakin technic, one is able to appreciate more fully the striking changes in the picture.

One of the surgical lessons which was really learned well in World War I was that primary wound closure was disadvantageous and actually contraindicated. It had an extensive trial and it was finally given up, except under ideal conditions. Early secondary closure, or delayed closure as we called it in World War I—a difference only in nomenclature—was practiced by Heuer, Pool and others at Evacuation Hospital I at Sebastopol, France, and Rene LeMaitre and DePage both recorded gratifying end-results in large numbers of cases handled by this method. The interval between debridement and wound closure varied from one day to six to ten days, depending upon local

conditions and depending also upon the bacteriologic findings, which then furnished the chief criterion for the decision

In World War II clinical criteria were largely substituted for bacteriologic criteria and proved entirely reliable. It is safe to assume that the properly conducted second stage of wound management in the base area, following a properly conducted debridement in the forward area, was at the heart of the very satisfactory mortality and morbidity statistics of the second World War.

Wounds of the Extremities Wounds of the extremities have always constituted a major proportion of all wounds in all wars. In World War II they made up approximately 83 per cent of all battle-incurred wounds. The number was increased first by the large numbers of fractures which occurred during the training period and second by the conversion of the Army to motor transportation and by the utilization of tanks in battle. I do not have the exact statistics, but it is my own belief that the fractures incurred in training programs, maneuvers and similar activities equalled, or perhaps exceeded, the number incurred by enemy action.

The picture of wounds of the extremities in World War II, as in all wars, was complicated by the frequent association of fractures with wounds of the soft parts and of blood vessels and nerves. The association was more frequent in this conflict than it had been in previous wars because of the high fire power of both artillery and bombs from the air, which had a wide range of devastation and which were far more damaging than similar agents used in World War I, when some sort of protection was possible against known shell trajectories.

The management of compound fractures in World War II showed remarkable improvement in the technical phases of management in forward hospitals and in the broad application of such procedures as early secondary closure or delayed internal fixation of mal-aligned compound fractures in base hospitals. The general concept, which was essentially sound, was that an injury to a bone should be treated on exactly the same surgical principles as an injury to any other tissue of the body. Furthermore, the program of management was predicated on the fact that all battle fractures must be regarded as septic, partly because they were usually associated with extensive damage to the soft parts and partly because they were so often received under conditions favorable to the introduction of foreign bodies and bacteria.

The program of management of compound fractures in their early stages was admirably summed up by Hampton. The spotlight, he noted, was removed from bacterial flora to the pathology of the open wound, and the surgical program was based on excision of dead tissue, whenever and wherever it was found, obliteration of dead space, or its dependent drainage, staged closure of the wound, atraumatic technic, with fine hemostats and ligatures, pressure dressings, adequate reduction and immobilization of fractures, precise splinting, and the adjuvant use of penicillin and whole blood.

These surgical principles were learned early in the war, in the North African-Mediterranean Theater. When they were applied to the large numbers of compound fractures received in the Normandy landings and elsewhere in the European Theater, and when they were supplemented by the great reduction in the time lag brought about by improved transportation facilities, the soundness of the new program of management was irrevocably affirmed.

Nerve Injuries Contrary to pre-war predictions, nerve injuries constituted nearly 10 per cent of all battle casualties in World War II. In numbers, in seriousness, and in the duration of the necessary treatment the neurosurgical was second only to the orthopedic load. It is still impossible, and perhaps never will be possible, to determine accurately the number of these wounds. I think it likely that the overall figure will be close to 100,000.

The management of a neurosurgical load of this size was a colossal task which was brilliantly initiated in the European Theater by Colonel Loyal Davis. When he returned to the States because of ill health, he was succeeded by Colonel R. Glen Spurling who carried the program through to a successful completion. Colonel Spurling then returned to the States as Consultant in Neurosurgery in the Office of the Surgeon General and in cooperation with Colonel Barnes Woodhall was responsible for the program in the neurosurgical centers which was so vitally important.

The collaboration and wise counsel of Dr. Jason Mixter, who served as Civilian Consultant in Neurosurgery to the Surgeon General's Office, is gratefully acknowledged as a fine contribution to the war effort.

The details of the highly successful neurosurgical methods used in World War II have already been recorded in detail in the literature and need no repetition. I would like, however, to comment briefly on three major categories of neurosurgical casualties, head injuries, peripheral nerve injuries, and injuries of the spinal cord.

The management of acute penetrating wounds of the brain in World War II followed with no essential modifications the basic concepts formulated by the late and great Harvey Cushing for the management of similar injuries in World War I. The neurosurgeons of World War II, however, unlike those of World War I, had almost perfect control of the infection which so often turned success to failure in the earlier war. Thanks to the sulfonamides, and later to penicillin, to liberal supplies of blood and plasma, and to rapid evacuation by air, Cushing's original principles were adapted to military circumstances in the second World War in a fashion which even that brilliant surgeon, with his imaginative outlook on neurosurgical problems, would not have dreamed possible in 1917 and 1918.

Perhaps the most important thing the neurosurgeons learned about head trauma in World War I—it was proved amply again in World War II—was that, unless the patient's condition were deteriorating, it was not necessary to hurry him into an emergency operation. He was, in fact, better for a delay which permitted adequate resuscitation and also permitted operation under an

optimum environment This policy reduced morbidity and prevented mortality It also had practical advantages for other wounded men The front line surgeons, with a clear conscience, could send patients with head injuries to the rear while they busied themselves with urgent cases in which delay could not be tolerated and while, in addition, they kept beds in the forward zone clear for urgent casualties

In one respect the most significant contribution made by Army neurosurgeons during World War II had to do with peripheral nerve injuries, since they constitute a problem which can be solved only in time of war In World War I the same opportunity existed but it was lost because no accurate or comprehensive follow-up studies were made In World War II that error was avoided Early in 1944 a Peripheral Nerve Registry was set up in the Surgeon General's Office, in which, by the end of the war, more than 8,000 peripheral nerve injuries had been entered Several interim analyses have already been made, and when, at the close of the appointed five-year period, the final analysis has been completed, the results of peripheral nerve surgery in World War II will be unequivocally clear and the pattern will be established for the proper management of similar civilian injuries

An extremely important, and certainly the most humane and dramatic, development in military neurosurgery in World War II was the program for the care and rehabilitation of soldiers with injuries of the spinal cord These casualties, in the acute phases of their injuries, were primarily neurosurgical problems and the neurosurgeons saw to it that every man with a penetrating wound of the spine had the benefit of prompt surgical exploration by experienced personnel Neurosurgeons, furthermore, worked unceasingly to expedite the transportation of these patients from forward hospitals to rear echelon installations adequately equipped for their treatment The transportation of casualties with spinal cord injuries, as I need not remind you, is a chapter of achievement in itself

I do not hesitate to assert that the reason so many of these tragically wounded men are alive today and are rehabilitated is the faithful and unremitting endeavor of all concerned in their care, beginning with the neurosurgeons, to supply prompt and expert treatment to them in the first phases of their injuries As soon as possible after initial surgery paraplegic casualties were evacuated to one or another of the 21 paraplegic centers in the Zone of the Interior Here a rehabilitation program was begun, based on the well recognized policies which had proved their effectiveness in civilian clinics but which were applied in the Army centers with an efficiency and zeal and sympathetic understanding that far surpassed any previous effort Great credit for the success of the program belongs to the individual urologists, orthopedic surgeons, rehabilitation and dietary experts, physical therapists and other specialists who shared with the neurosurgeons the responsibility for it Even more credit belongs to them as a group, for they provided an example of wholehearted, efficient medical and surgical cooperation that is unique in Army and

civilian practice alike I think they have had their reward The ultimate goal of the Army paraplegic program was to enable every such casualty to resume his former place in civilian life It is a source of happiness and satisfaction to all who participated in the effort to realize that that goal has been achieved beyond what any of us dared to hope

Vascular Injuries The number of patients with vascular injuries received in the Zone of the Interior from the combat areas so far exceeded all expectations that the establishment of centers for their specialized care was almost inevitable The vascular center at Ashford General Hospital, which logically was headed by Colonel Daniel C Elkin, with his long-time interest in vascular and cardiac injuries, served as a sort of pilot plant for the centers at Mayo General Hospital, under the direction of Colonel Harris B Shumacker, Jr, and at DeWitt General Hospital, under the direction of Colonel Norman E Freeman The astonishingly low mortality achieved in these centers—four deaths in 803 operations for aneurysm and arteriovenous fistula, for instance—and the equally remarkable functional results, are all the testimony one needs as to the wisdom of the policies adopted in this field of surgery

It ought to be emphasized that far more than vascular injuries became the business of the vascular centers Well over a thousand patients with cold injuries, chiefly trench foot, were treated at the Ashford Center alone, and all three centers have to their credit a brilliant record of treatment of this condition, a record which counterbalances, so far as that is possible, the unhappy record of its prevention, or, more correctly, of the failure to prevent it I need not remind you that the incidence of trench foot in the Mediterranean and European Theaters is one of the blots on the Army record in World War II though I feel perfectly justified in adding that if the warnings of the Surgical Consultants Division had been heeded by Command the record would have been quite different

A significant and important phase of the work of the vascular centers was the investigative program carried out, in one form or another, at each of them The clinical and physiologic studies which were made will be of lasting usefulness in the management of civilian vascular diseases As the result of these investigations, many of the problems in this field which had hitherto been unsolved, or the solution of which had been based on little more than speculation and presumption, were solved or are well on their way to solution

Equally important are the follow-up studies now being carried out under the direction of the National Research Council and with the cooperation of the Veterans Administration The critical evaluation of late results is of greater worth because of the continuous detailed observations made upon these men from the time of injury

I have little doubt that these various studies will remain one of the largest and most successful contributions which will ever be made to the knowledge of the pathologic physiology of vascular injuries and of their management

Abdominal Injuries Abdominal wounds are always the most serious of battle injuries because they are seldom simple. It is the exceptional case in which only a single viscus is injured. Wounds of the small intestine are almost always multiple and are frequently associated with damage to the large intestine and to the bladder, kidney and spleen. Moreover, 10 per cent or more of all abdominal wounds are abdominothoracic, a variety which is far more serious and more difficult to manage than wounds confined to the abdomen.

These generalizations all apply to the abdominal injuries encountered in World War II, and it is therefore pleasant to be able to report that while the mortality for these wounds in World War I was between 60 and 75 per cent, in World War II it was reduced to between 25 and 35 per cent, although the percentage of operability was the same in both conflicts. The improvement is clear proof of what earlier surgery and better methods of resuscitation can accomplish.

As to methods, no outstanding changes in technic were developed in World War II, though it did become routine to exteriorize all wounds of the colon, except those of the cecum and ascending colon, which could be handled, like wounds of the small intestine, by primary suture. It also became routine to perform colostomy in all wounds of the rectum, with a considerable improvement in results because the diversion of the fecal stream reduced the amount of infection.

Early in the war it was customary to introduce sulfonamides into the peritoneal cavity in all abdominal wounds. This method was soon found to be fraught with considerable danger of adhesions and of intestinal obstruction, and it was abandoned by order later in the war.

Damage to the kidney and spleen usually called for splenectomy and nephrectomy. Wounds of the liver were rapidly fatal in a high proportion of cases, though at that, a surprising number of lives were saved by immediate operation. The control of hemorrhage was the immediate objective of laparotomy, which was performed whenever the casualty survived long enough to permit it, for enormous damage was done to the parenchyma of the liver, especially if the missile had been fired at short range.

The mortality of abdominal wounds is difficult to evaluate and statistics are frequently misleading because of the multiplicity of wounds and the circumstances of wounding. There is no doubt, however, that the lives saved in this type of injury in World War II can be attributed to adherence to the principles just outlined and to a postoperative regimen in which skilled nursing care was supplemented by nasogastric suction, chemotherapy and antibiotic therapy, the lavish use of blood, and the correction of protein and vitamin deficits.

Thoracic Surgery The first substantial advances in the field of thoracic surgery, regardless of the lesion, occurred in World War I. In the interim between the wars important contributions from various surgical clinics all over the world established the feasibility of this branch of surgery, and World

War II furnished an enormous clinical laboratory in which to test old and new concepts

The final statistics on injuries of the chest in World War II are still to be compiled, but it is safe to say that they will prove considerably lower than in any previous war. In 1944 Carter and DeBakey reported a mortality rate of 81 per cent in more than 20,000 chest wounds treated up to that time, against a mortality for similar injuries in World War I of 24.5 per cent.

It is tempting to attribute these results to the adoption of new and radical operative procedures perfected between the two world wars, but it would not be true. Actually, lobectomy, pneumonectomy and other radical thoracic operations found little place in the treatment of wounded men. Refinements in surgical technic and the availability of chemotherapeutic and antibiotic agents and of large supplies of blood had much to do with increasing survival rates. More important were the judicious timing and the proper selection of surgical procedures, and still more important were adequate resuscitative measures. No patient was operated on until shock was controlled and his condition was stabilized. There was full appreciation, moreover, of a feature peculiar to chest wounds, that partial suffocation can be a major factor in producing shock when intrathoracic structures are injured. It was soon discovered that a rapidly fatal outcome could be expected if accumulations of blood or mucus in the trachea or bronchi were not promptly removed by catheter suction or bronchoscopy. The so-called wet lung was an even more serious problem, for which the liberal administration of oxygen furnished the best solution.

In World War II the chief emphasis was placed on the status of the intrathoracic organs. Less attention was paid to the thoracic wall, unless an open sucking wound was present, when, of course, immediate closure was carried out. Another important consideration in respect to the chest wall was the control of pain originating in it from fractures or other injuries. Injections of procaine at the site of the injury were effective, and paravertebral block gave even better results. These simple measures were far more important than they might seem, since the control of chest pain played a major role in the management of shock in thoracic wounds, and since the strapping ordinarily used for such lesions in civilian life was found to cause a dangerous reduction in vital capacity when it was employed in casualties with extensive chest wounds.

Another lesson learned from the recent military experience was that the conservative management of hemothorax practiced in civilian life has no place in the management of severe battle-incurred thoracic injuries. The idea that the early evacuation of blood from the pleura was not only not necessary but might result in secondary hemorrhage was quickly overturned. The prompt evacuation of the hemothorax, without air-replacement, permitted the re-expanded lung to occupy the pleural space, and if empyema did occur, it was practically always of small volume. Failure to evacuate the hemothorax, how-

ever, was likely to be followed by the development of a chronic hemothorax or fibrothorax and by later secondary infection

For many years after World War I the wards of Army hospitals were filled with respiratory cripples. Some of them were suffering from pyogenic empyema secondary to pneumonia, but many others could thank the ultraconservative treatment of traumatic hemothorax for their condition. We are not witnessing any such unhappy situation today. Chronic empyema was actually rare in World War II. Antibiotics and chemotherapeutic agents controlled pyogenic empyema, the proper surgical management of traumatic hemothorax practically eliminated serious chronic pleural abscesses, and decortication of the lung, as revived by Burford and others, took care of clotted hemothorax. The ultimate objective of the management of hemothorax was early, complete re-expansion of the lung, with conservation of as much cardiopulmonary function as possible. It was achieved in a truly remarkable number of cases.

A word must also be said about the large number of thoracic lesions observed in World War II which were not of combat origin. Thousands of cases of bronchiectasis were seen, most of them not related to chest wounds. Many of them were treated by surgical extirpation of the diseased lung tissue. The remarkable accomplishment of Meade, Kay and Hughes, who performed 196 lobectomies, chiefly for bronchiectasis, with only one death, at the Kennedy General Hospital Thoracic Surgery Center, was more or less duplicated at the other thoracic centers.

Intrathoracic tumors, which were also discovered in surprisingly large numbers, were treated earlier than in any comparable series in civilian life, because routine roentgenograms of the chest were made when the soldier was inducted into the Army and again when he was ready for discharge. Regrettably, many of the cases of bronchiogenic carcinoma discovered, usually by accident, in these young men were inoperable. On the other hand, the results in mediastinal tumors were extremely encouraging. Blades, for example, reported 109 cases at five Army hospitals over a three-year period without a single surgical death in the resectable lesions.

It must be borne in mind, before we congratulate ourselves too heartily on the dramatic advances in thoracic surgery during World War II that the subjects of the operations, whether they were performed for wounds or for diseases of the chest, were usually young men, and, more important, young men who had not withstood the ravages of chronic pulmonary disease. We can scarcely expect that the lower mortality rate achieved in this group can be duplicated in civilian life, in which thoracic surgery is chiefly performed in an older age group, with advanced disease. The lessons learned in the care of severely wounded soldiers, however, and the experiences gained during the war in surgical diseases of the chest, have furnished information which will be invaluable when it is applied, as most of it can be, to the management of diseases and injuries of the chest in the civilian population.

The organization of the thoracic centers in the Z I was directed by Colonel

Brian Blades whose sound advice to the Office of the Chief Consultant in Surgery was invaluable and to whom I make a sincere acknowledgment of my appreciation

Plastic Surgery In the 300-page record of plastic surgery in World War I, skin grafting is mentioned in a single sentence Burns are not mentioned at all In World War II at least a third of the work in plastic surgery concerned free skin grafts, and about a third of it was carried out for burns

It must be granted, however, that modern plastic surgery received its first real impetus in World War I and that the lessons learned in the course of it were later transferred to civilian use In all probability the evolution of the management of burns can be attributed to the results achieved in the Cocoanut Grove disaster in Boston in December, 1941, shortly after the United States had entered World War II The sound conclusions drawn by the men who treated those casualties formed the background of the management of burns in the second World War, when the increased use of combat motor vehicles, both on land and in the air, made the care of these casualties a serious problem clinically, while the numbers of casualties with these injuries required their management on a mass basis

We were greatly assisted, in setting up the plastic surgery program, by Dr Jerome Webster, Dr Robert Ivy, and the late Dr John Staige Davis, who gave unsparingly of their time and effort and who responded to every call To Colonel James Barrett Brown, however, belongs more than to anyone else the credit for what American plastic surgeons achieved in World War II In 1942 he was ordered to the European Theater, to study the casualties which had occurred as the result of the brief struggle on the Continent and the continuing blitz warfare

When he returned, he served both as chief of the plastic service at Valley Forge General Hospital, the first of the plastic centers to be established, and as advisor in plastic surgery to the Chief Surgical Consultant in the Office of the Surgeon General

But tribute must also be paid to all the other plastic surgeons They performed some 40,000 operations without a death They were always numerically in short supply, but they carried an enormous burden of work—at one time 33,000 operations were scheduled for performance on the 11,000 patients then in the eight plastic surgery centers in the Zone of the Interior Many of these highly skilled surgeons had to be kept in the Army for a year or more longer than their associates, long after they could have been released on points, because the work they were doing could be done by no one else

When I asked Colonel Brown to outline for me what he considered the highlights of his specialty as it was practiced in World War II, he listed the following points

- 1 The elimination of tannic acid in the management of burns and the substitution of atraumatic care of the wound, the use of pressure dressings to prevent loss of serum, and early skin grafting

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2 The early closure of wounds, either by grafting or by suture, with or without the utilization of flaps

3 The establishment of specialized centers and of specialized teams in the combat zone for the immediate care of casualties suffering from burns and facial injuries The superior functioning of these services cut down very materially the time required for the definitive and long-drawn-out plastic repairs to be done in the Zone of the Interior

4 The extensive use of local tissue in repairs

5 The fundamental principle of wound closure, which was highly developed by plastic surgeons and which was used in many cases preliminary to secondary orthopedic or neurosurgical procedures on the deeper tissues

6 The concept that deep healing can be no better than superficial healing

7 The close cooperation of plastic surgeons with dentists, anesthetists, orthopedic surgeons, neurosurgeons and the nursing service in the management of their casualties

8 Special procedures devised for the management of injuries in particular regions, including the palate, the jaw, the nose, the ear and other parts of the face, the lower extremities and the hands

As Colonel Brown well expressed it, the miracles of reconstruction performed by the plastic surgeons would have been impossible without the courage and the will to live displayed by these young men who seemingly had been marred for life, and without the industry and confident hope of the surgeons who restored them to lives of useful activity Medical history has no finer example of the doctor-patient relationship, and plastic surgeons have every right to be inordinately proud of what they accomplished

LOOKING FORWARD

As one looks to the future, the conclusion seems inevitable that if war comes the menace of the atomic bomb plus the addition of new technics will make it a more horrible and devastating conflict than any which has preceded it It will bring into the zone of destruction all civilians as well as members of the military establishment

The introduction of atomic weapons wipes out many of the old concepts of war, erases zones of security, and makes combat truly global A declaration of war would be followed immediately by a huge number of casualties, largely civilian, such as no battle between military forces has ever produced

"We shall be left literally with 'No Place to Hide'," as Bradley has said in his remarkable book of that title "Bikini," he points out, "is not merely a ravaged and useless little atoll in the deep far Pacific Bikini is our world"

War would require the immediate and rapidly complete mobilization of the entire medical personnel of the nation on a disaster basis and indeed should require a mobilization of our entire citizenry, a step imitating totalitarian methods but definitely necessary and I believe certain to be invoked when and if combat fully develops

It must be recognized that as war develops air power takes an increasingly prominent part, and while it may be argued by the military that the atomic bomb has not greatly changed basic military principles nor obviated many of the conventional roles of military forces, supersonic planes, guided missiles, and radar controlled guns guarantee an immediate scope of action and a destruction of both humans and war potentials never before dreamed of. Air attacks will be followed by invasions and counter-invasions, the ensuing warfare, we are told by Groves, will then be orthodox in principle but not in detail. The Army still insists that all efforts of the military team are for the breaking of the enemy's resistance and the final advance of ground troops onto enemy soil. Naturally such widespread operations, so devastating in character, so unorthodox in execution, will call for leadership both in the field and in the rear echelons far greater than in the past.

To the end that some plans be formulated and some attempts be made to avoid the almost complete absence of medical plans such as happened in World War II, it is essential that the medical profession coordinate its efforts and assume leadership for an over-all plan. Certainly the armed forces branches snarling at each other and grasping to forward each its own department are ill-fitted for and incapable of this over-all planning. Clemenceau is said to have remarked that war was too serious a business to be left entirely to the military. Perhaps he meant to intimate that the politicians were more able to meet the inevitable problems of conflict. He must have known that Clausewitz defined war as the employment of organized violence to obtain political goals.

All this is to say that civilian agencies will and should dominate the direction of all efforts, certainly at the beginning of another conflict. From the medical standpoint the military must be properly supplied with doctors but, and I emphasize this, only after a proper integration with civilian needs and resources. This overwhelming responsibility should be apparent, I think, to all medical men and I deprecate the laissez-faire attitude which seems to pervade our country at the present time. True, the military establishment is making efforts to put into effect some of the concepts thrust upon it in the recent war, but the process is slow and fitted only for the military establishment itself.

The changing pattern of warfare of World War II developed a new military philosophy whereby the major efforts of destruction were aimed at war making potentials and particularly industrial resources. This change out-modes the modern army's Tables of Organization in so far as medical troops are concerned.

The Council on National Emergency Service of the American Medical Association has advocated two developments within the Defense Establishment. The first is "a permanent board of top flight civilian physicians working arm in arm with the Surgeon Generals at high enough level within the military establishment to supersede the uninformed and often arbitrary authority of command." The second is "a group of civilian physicians at top level within

MISSION ACCOMPLISHED

government having the responsibility of weighing the medical man power needs of industry, agriculture and the civilian population at large, of research, public health work and medical education against the requirements of the military establishment "

Such planning is all very well but I venture to question its practicability I see no particular advantage in going "arm in arm" with the Surgeon Generals of the armed forces until they are given authority in medical matters which is now exercised by officers of the Service of Supply and of the line

Also, within a few months the Voorhees Report published by the Hoover Commission has been made available to the public and it is worthy of careful scrutiny and consideration by all medical men It reflects mature judgment and sets down on paper recommendations which are so sound, so saving of personnel, materiel, and funds that it is easy to join in the fervent hope of its adoption in large part

It is a long step in the right direction but it applies to federal agencies only, including the armed services, whereas coverage of the entire population is demanded Obviously this calls for planning on a high level and with authority As of today there are no plans and there is no authority The problems which will confront medicine in the future, and particularly war medicine, will be overwhelmingly greater than those of World War II

The introduction of atomic weapons may possibly change the entire concept of the surgery of trauma It certainly will introduce new problems for the treatment of irradiation, blast injuries and burns It will call for an entirely different type of cooperation between military and civilian authorities Perhaps there will be little distinction between the medical responsibilities of the two It may change the entire plan of medical practice Such possibilities demand realistic thinking, courageous, unselfish patriotism and a high order of statesmanship The uncertain future should make us hasten to digest the lessons of the last war, integrate civilian and medico-military agencies, and thereby be an advantage to our position in the event we are again drawn into world chaos

In the words of Winston Churchill, "We must preserve and if the gulf continues to widen, we must make sure that the cause of freedom is defended by all the resources of combined forethought and superior science Here lies the best hope of averting a third world struggle, and a sure means of coming through it without being enslaved or destroyed "

To this end we should dedicate ourselves, laying aside prejudices and self-seeking and standing fast by the humanities which are the only bulwarks against ultimate disintegration of culture and civilization

CANCER OF THE BREAST*

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WE ARE IN THE PROCESS of studying in detail the cases of carcinoma of the breast that were seen at the University of California Medical Center from July 1, 1930, to January 1, 1944. A total of 819 cases were seen in the hospital or out-patient clinic. In 83 cases no treatment was given here, but the patients have been followed. The remaining 736 patients had some form of definitive or palliative treatment. In our analysis we have used Schenck's classification¹. It is questionable whether this is the best method of classification, but it seems to be the one in general use in the literature. In our series 173 cases, or 21 per cent, were classed as stage I. There were 201 cases in stage II and 203 in stage III. Thus, approximately half the patients were first seen when their cancer had spread to the axilla or was already far advanced. One hundred six patients (13 per cent of the series) who had had previous surgery elsewhere came to us for treatment of a recurrence (stage IV). In 53 cases roentgen ray therapy was given at our clinic following operative treatment elsewhere. Eighty-three patients who had been treated elsewhere were seen in our clinic for follow-up only. Of the entire series of 819, six patients were lost to follow up †.

There is such a difference of opinion in the literature today it is difficult to judge what is the best method of treatment for operable cancer of the breast. In a large general hospital handling both clinic and private patients, no definite routine can provide the specific treatment for each individual case. Our patients come from all parts of the state. Some have had a biopsy or local excision of the tumor before being referred to the clinic. It is obvious that many patients will come to us too late, nevertheless, these people still have hope and expect that we can cure them. It seems to me that we should accept every patient with cancer of the breast as one of our responsibilities. Regardless of the favorable statistics in one small selected group, we should consider what we are able to do for all patients with cancer of the breast who come to us for treatment. In our series of 819 cases, 264 patients were living and well five years or more after treatment, a survival rate of 32.2 per cent (Fig. 1). This figure does not include operative deaths or cases in which death in less than five years was due to intercurrent disease. There were four operative deaths in 470 primary surgical cases, a mortality of 0.85 per cent.

Of the group in stage I, 61.8 per cent survived five years or more regardless of the type of treatment. The five-year survival rate in stage II was 39.8 per

* Read before the American Surgical Association, St. Louis, Mo., April 20, 1949.

† This is due entirely to the diligence and hard work of our follow-up secretary, Mrs. Elnor Wells, to whom we are indebted for the completeness and accuracy of our statistics.

CANCER OF THE BREAST

cent, and in stage III, which comprised the advanced cases, it was 83 per cent. In these three groups which include all cases of primary carcinoma, 105 patients had roentgen ray therapy alone which in most cases was palliative. Of the 470 patients in whom a definite attempt at cure was made by surgery with or without radiation, 201 lived five years without recurrence. Thus, the five-year survival in operable cases was 42.8 per cent. In stage IV, of 106 patients who had a recurrence of a carcinoma that had been operated upon elsewhere, 24 (22.6 per cent) were living and well five years or more after treatment. In stage V, the group who had surgery elsewhere followed by roentgen ray therapy at the University of California Hospital, there were 53 living and well

FIG 1

ALL STAGES SEEN OR TREATED 7130 TO 1149				
Number	L and W 5+ Yrs	Lost to Follow up	Percent Lost	Mortality
819	32.2%	6	78%	4 Cases 85%

STAGE I- AXILLA NEGATIVE 173 CASES		
Treatment	No	L and W, 5+Yrs
Radical Surg Alone	101	70.3%
Rad Surg + Preop X Ray Therapy	22	54.5%
Rad Surg + Post op X Ray	22	68.1%

FIG 2

FIG 2—The other 28 cases are the patients either treated by simple mastectomy, roentgen ray, or lost to follow-up

over five years, or 39 per cent. In stage VI, of 83 patients who were followed in our clinic after treatment elsewhere, 15 (18 per cent) lived five years without recurrence.

One of the puzzles of the problem of cancer of the breast is why we fail to obtain a 100 per cent cure in patients with a localized lesion without evidence either clinically or pathologically of axillary spread. It must mean that there is already extension of cancer cells that we are unable to detect at the time of surgery, or that some cells are spread during the surgical procedure. It is also curious that some of these patients have a recurrence after many years of apparent cure. We wonder where the malignant cells have been all the time and why they wait 10, 20, or even 30 years before becoming evident. The latest recurrence in my personal experience was in a doctor's widow who, 27 years after radical mastectomy, had a recurrence in the scar. She has now lived five years since resection of the recurrent tumor. Is there such a thing as cancer immunity that in some patients holds the growth in check and then for some reason is lost, allowing the cells to grow? If we had some chemical way of determining this we might be better able to cope with the disease.

McWhirter² has aroused considerable interest as well as controversy by recommending a simple mastectomy followed by postoperative roentgen ray therapy. His idea is that if the axilla is not involved there is no need to do a radical axillary dissection, and if the tumor has spread to the axilla, removal of this natural barrier, together with the trauma inflicted on the involved tissues, may well allow dissemination of cancer cells to distant sites. He reports the five-year survival rates for all operable cases treated during a ten-year period

FIG 3

STAGE 2 - AXILLA POSITIVE 201 CASES		
Treatment	No	L and W 5+Yrs
Radical Surg Alone	90	40%
Rad Surg + Preop XRay Therapy	43	41.6%
Rad Surg + Post op XRay	37	24.3%

STAGE 3 - AXILLA POSITIVE ADVANCED 203		
Treatment	No	L and W, 5+Yrs
Radical Surg Alone	12	16.6%
Rad Surg + Preop X Ray	15	20.0%
Rad Surg + Post op X Ray	16	18.7%
X Ray Alone	103	2.91%
Simple + Post op X Ray	14	21.4%

FIG 4

FIG 3—The other 31 patients were treated by simple mastectomy, roentgen ray, or lost to follow-up.

FIG 4—The other 43 patients were treated by simple mastectomy alone or were lost to follow-up.

tioners refer all cases of cancer to the Royal Infirmary in Edinburgh, he may be getting his cases earlier and therefore have a larger percentage in which the cancer is still localized in the breast.

We have hoped that by the use of adequate roentgen therapy either before or after operation we could increase the number of five-year survivals, particularly in stage II. Statistically, the possible benefits of roentgen ray therapy are not reflected in the five-year survival rate. In stage I (Fig 2) the highest five-year survival was in those patients who had radical surgery alone. In stage II (Fig 3), the slightly higher survival rate with the use of preoperative roentgen ray therapy is probably not significant. Figure 4 shows that in

From 1941 to 1945, when his main method of treatment was simple mastectomy with postoperative roentgen ray therapy, he had a total of 941 cases with a five-year survival rate of 55.9 per cent. This is significantly higher than that achieved during the period 1935 to 1940 when the main method of treatment was radical mastectomy and postoperative roentgen ray therapy. During this period 569 cases were treated with a five-year survival rate of 44.0 per cent. One would like to know how many of his cases were really stage I, since with simple mastectomy there is no microscopic examination of lymph nodes, and we know from experience that our judgment of the presence or absence of cancer in the axilla on clinical examination alone is wrong 30 per cent of the time. McWhirter's views are so contrary to the teaching in this country that one would hesitate to adopt this course without further proof that it is the procedure of choice. By making a special effort to have general practi-

stage III the use of radiation resulted in a somewhat larger percentage of five-year survivals. In this group, of 14 patients who had simple mastectomy plus postoperative roentgen ray therapy, 21.4 per cent were living and well five years later, as compared with 16.6 per cent of patients who had radical surgery alone. If a greater number of cases were represented, this might point more toward confirmation of McWhirter's ideas. Figure 5 shows the results in these three stages combined. It is seen that in the entire group the use of preoperative or postoperative roentgen ray therapy does not increase the number of five-year survivals. In another five years, with a larger series of cases, the roentgen ray therapy may show up to better advantage.

COMBINING THE THREE STAGES 557 CASES		
Treatment	No.	L and W, 5+ Yrs
Radical Surg Alone	203	53.6%
Rad Surg + Preop X-Ray	80	41.2%
Rad Surg + Post op X-Ray	75	36.0%
X-Ray Alone	105	2.8%

FIG 5

FIG 5—The other 94 patients were treated by simple mastectomy either with or without roentgen ray or lost to follow-up.

TEN YEAR SURVIVAL REGARDLESS OF TREATMENT 7-1-30 TO 1-1-49		
Stage	Number	Percent
1	37	56.9
2	27	28.4
3	0	0
1 and 2	64	41.8

FIG 6

FIG 6—These figures and percentages are figured for the total group of 1177 cases from July 1, 1930 to January 1, 1949.

The ten-year survival rate for stage I and stage II for the period July, 1930, to January, 1939, is shown in Figure 6.

We were interested in determining whether the incidence of swelling of the arm after radical mastectomy was increased with the use of roentgen ray therapy. In our series there was no significant difference. Marked swelling occurred in 11 (3.4 per cent) of the surgically treated cases, and in 13 (5.8 per cent) cases in which surgery was supplemented by radiation therapy. In none of these patients was the swelling incapacitating.

SUMMARY

From our study so far, roentgen ray therapy as an adjunct to the surgical treatment of carcinoma of the breast has not significantly increased the five year survival rate. The study will be continued.

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DISCUSSION—DR. WILLIAM CRAWFORD WHITE, New York City I am a little hesitant about coming up to speak because, like Doctor Bell, I feel that I know less about this disease than I did after my first paper in 1921

However, I have been interested recently in a study of some of the factors that perhaps are important in the surgical approach I think it is generally agreed that we should follow out the Halsted principle, to the effect that we should remove the breast, the pectoral muscles, and the axillary contents, but there is no agreement, as far as I can discover, as to the amount of skin to be removed, the necessity of skin grafts, and the methods of undercutting the skin in a peripheral dissection

I do not need to go into details, but all of you here know of the various arguments that are presented on this point There are some surgeons who are convinced that one must undercut the skin well out, leaving no fat attached to the cutis, and that therefore their results will be better

I thought that an answer to the problem would be given by a study of local recurrence It seems to me that a report on the percentage of local skin recurrences in five years, in cases in which the disease is confined to the breast, would be a good measure for comparison We also recognize that the accuracy of the diagnosis of localized cancer is dependent on the enthusiasm, zeal, and intelligence of the pathologist Under such a man, the number of Group I cases will be smaller, and the local recurrences less

A review of the reported five year local recurrence rates in various clinics, in cases of localized breast cancer, fails to prove the contention of proponents of extreme undercutting with skin grafting that their method is superior

I think a very good point was made by Oliver and Sugarbaker, who said, "decreasing the incidence of skin recurrence would appear to be dependent among good surgeons not on the commonly discussed variations in surgical technique, but on the earlier diagnosis and surgical treatment, and on the adherence to leaving a narrower criteria of operability"

We have been convinced from some work that we did at the Roosevelt Hospital in New York that there is another factor Brandes and I have demonstrated that quite frequently we have cancer cells on the gloves which are used in the operation Saphir of Chicago has demonstrated cancer cells on the scalpels that were used These loose cells may very well be an important factor in the incidence of local recurrence

DR GRANTLEY W TAYLOR, Boston It is very gratifying to hear Dr Bell's paper We realize that his results are entirely in agreement with the experience of most others who are engaged in this work I think the differences which obtain are more apparent than real

The selection of cases suitable for operation is of the utmost importance Dr Haagensen, of New York, tried to define these criteria recently They are very much sharper, and all of us, as we do more breast surgery, I believe, are inclined to discard some of the cases which are borderline and in which we know we cannot bring about a fair result by surgery

It is very difficult even to compare hospitals in one community and another on the basis of the total operability rate We had the experience in Massachusetts when they opened the State Cancer Hospital for terminal care in advanced cases, that our operability at the Massachusetts General Hospital increased and improved very much It wasn't a relaxation of our criteria of operability—it was the selection going on in the community which chose more favorable cases to send to us We are primarily a surgical hospital, and send all the advanced cases to the Cancer Hospital In spite of that, our operability roughly has maintained itself through the years because we have correspondingly been sharpening our criteria

I want to emphasize what Dr White said about the zeal of the pathologist in looking for axillary metastases Obviously, if they select only those cases without any

axillary involvement after a very thorough search, the results will be better than if that examination is purely perfunctory. Similarly, the inclusion of a number of cases with very minute axillary involvement in Stage 2 group will improve the results in that series.

We have plowed back and forth the problem of postoperative and preoperative x-ray radiation, and we are unable to demonstrate that it gives any advantage. We also have given thought to the problem of whether the wide skin removal, which Dr White referred to, is necessary. We are unable to demonstrate that any advantage accrues to the very extensive procedure of the classical Halsted type.

Finally, I think one thing should be weighed very carefully, namely, the complications of postoperative radiation. I noticed with some disturbance and distress that the incidence of swollen arm is a very serious problem in some clinics. Dr Treeves, of Memorial Hospital, incidentally referred to swollen arms as occurring in about 70 per cent of postoperative radical mastectomies. I cannot believe that is a true statement of incidence, because I don't see why it should happen unless it is because of the postoperative radiation.

The incidence of swollen arm in our clinic is less than 10 per cent. Dr MacDonald recently reported from California that he had some 50 per cent of appreciably swollen arms in his series of breast cases, and he has recommended resection of the axillary vein with the idea of preventing this.

I am inclined to think that some of that may be due to postoperative x-ray, which helps to obliterate some of the residual lymphatic branches.

DR OWEN H. WANGENSTEEN, Minneapolis: Mr. Chairman and Gentlemen, I am not an experienced breast surgeon, but I have been interested in the aggressive therapy of cancer. I do not believe real improvement will come from attempting to refine upon refinement, but as long as we have to deal with late cancer I believe that our only hope is for the surgeon to be more aggressive.

I have felt on occasion, and I suspect many of you have felt similarly in attacking cancerous lymph nodes extending up along the axillary vessels to the point where the vessels pass over the first rib, much like a hunting dog must feel when he is chasing a pheasant and the pheasant flies over a fence. The surgeon has the alternative, of course, of taking the fence down.

I have three slides which I would like to show and comment upon briefly.

(Slide) This is the first patient upon whom I operated, a patient with axillary metastases. As long as there is such a big discrepancy in the results of operation cases between Stage 1 and Stage 2 cases I think it is incumbent upon the surgeon not to retract but to expand the amplitude of our operation in Stage 2 cases.

This patient had large axillary metastases, but upon resecting the clavicle and removing the first rib six additional metastatic lymph nodes were found beyond the reach of the conventional axillary dissection. One involved lymph node was found in the brachial plexus, another at the site of juncture of subclavian and internal jugular vein, two along the inferior border of the innominate vein, and one in the second intercostal space. Moreover, in the conventional axillary dissection, the component cords of the brachial plexus can be separated. This dissection does not appear to cause areas of paresthesia or any untoward effects.

I submit that one of the weaknesses of the present so-called Halsted operation is our inability to get cancer out of the brachial plexus. I believe that by dividing the clavicle and putting it together again, and removing the first rib, in Stage II cases one can dissect the components of the brachial plexus just as well as one can the axillary vein, and there is no need to resect the axillary vein, because both the axillary vein and artery can be exposed over about a 15 cm length and their fascial sheaths may be removed also. Careful stripping of the adventitia of the axillary vein and artery

as well as the brachial plexus over long lengths, I believe should come to be standard practice in the conventional radical breast operation

For the patient with definite axillary metastases, I am proposing to divide the clavicle, removing the first rib, in order to permit extension of the operation in Stage II cases to include the following in addition to the conventional radical (1) supraclavicular dissection, (2) removal of the greater length of the internal mammary vessels beginning at their sites of origin, (3) dissection of the upper mediastinum, stripping the homolateral innominate vein in instances in which lymph node involvement beyond the first rib is observed

(Slide) I have had experience so far, however, with only five cases. This slide indicates how the clavicle is put together with an intramedullary Kirschner wire. Patients with an intact clavicle have considerably less postoperative deformity. Moreover, they appear to have less difficulty in breathing in the early postoperative phase than does a patient in whom the inner portion of the clavicle has been excised.

(Slide) This slide shows a patient who was alleged to have a metastasis in the lung. A rounded hazel nut-sized nodule can be seen in the lateral film up against the sternum and fairly close to it. This patient had no extension beyond the conventional axillary lymph nodes. The pulmonary metastasis proved to be a fibroma in the lung.

I am certain that most of you are familiar with the writings of R. S. Handley, the son of Sampson Handley, and his associate, Thackray, at Middlesex Hospital, London. They have been removing (as Handley's father suggested in the late '20s) the lymph node along intercostal vessels in the second interspace. By making a short transverse extra pleural incision along the sternal margin in the second and fourth intercostal spaces, the greater length of the internal mammary vessels can be removed and the lymphatic tissue in juxtaposition to them.

It is too early to say what, if any, improvement will come from all this. Those of us who have had the opportunity of comparing the results of the abdominoperineal operation for low lying cancers of the rectum (6 cms or less from the anus) with those in which the anastomotic operation is performed are aware that there is a difference—even in Stage I or so-called Dukes' group A cases without demonstrable lymph node involvement. There is an advantage in removing the *entire* lymphatic drainage area for a cancer because failure to demonstrate lymph node involvement is not synonymous with absence of small microscopic deposits. Our failure to cure 100 per cent of Stage I breast cancers is owing in part to the circumstance that there are now and then microscopic lymph node deposits beyond the site of lymph node removal, and in part to the occurrence of direct venous invasion. Moreover, I think the time is not far away too when we will hesitate less over the sacrifice of the other breast, for the systemic influence which occasioned the initial breast cancer probably continues to operate.

DR ROBERT M. JANES, Toronto: I should like to express a somewhat different opinion than that to which we have listened.

It has been my privilege to conduct, along with the Department of Radiotherapy at the Toronto General Hospital for the past fifteen or sixteen years, a joint breast clinic. We have analyzed our results, and they show the variables that creep in, but we feel increasingly convinced that preoperative radiotherapy plays an important part.

We all know that the results of different surgeons vary at least 10 per cent, and I am sure the efficiency of radiotherapy varies at least as much.

I have slides of two patients, each operated upon eleven years ago that illustrate the results that have been obtained with preoperative radiotherapy followed by radical mastectomy.

(Slide) This is the first slide of this patient. Notice the massive involvement of the axillary lymph nodes.

(Slide) After preoperative radiation

CANCER OF THE BREAST

(Slide) Six years later Radical mastectomy after the reaction to radiation had subsided enough to justify it The patient still remains free of evidence of disease

(Slide) This is the first slide of the second patient, eight months' history Extensive ulcerating carcinoma of the breast, with axillary lymph node involvement

(Slide) This shows the lesion almost healed following preoperative radiation

(Slide) This slide was taken five or six years later The patient is still free from clinical evidence of disease

These slides can be duplicated many times We have become increasingly convinced of the value of preoperative radiation and are employing it to a greater extent than in the past

DR H GLENN BELL, San Francisco I wish to thank all of the discussers for their remarks Dr White, in our clinic we have one young man in training in surgery who is the type of chap that is always asking embarrassing questions Some time ago he came to me and wanted to know "What is an adequate skin margin in carcinoma of the breast? You give a carcinoma of the lip a centimeter and a half and say that is quite adequate Why do you say to give a hand's breadth to a breast tumor?" He went around and measured a lot of people's hands, and he found that hands don't measure the same, so he is questioning what is an adequate skin margin He didn't stop at that He is now working in the laboratory, taking almost serial sections of carcinoma of the breast, to find out how far from the tumor one might have to go before he can say, "This is an adequate skin margin" I, too, have found that the statistics are very difficult to compare around the country

I did not mention (though it will appear in my paper) the incidence of swollen arms in our clinic We, too, have the feeling that postoperative x-ray therapy particularly would increase the number of swollen arms There is not much difference We divided them into mild, moderate and marked swelling In the group that had postoperative radiation we have 65 per cent who had marked swelling, as contrasted to 32 per cent that had markedly swollen arms without x-ray therapy None of these arms were swollen to the point that they incapacitated the patient It did not hinder the patients' work

MALIGNANT MELANOMA*

FORTY CASES TREATED BY RADICAL RESECTION

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SINCE THE FIRST RECORDED description of a pigmented nevus by Hippocrates,¹ melanomas have been a source of interest to physicians throughout the world Dupuytren² is said to have been the first to recognize melanosis as a clinical entity, but Laenec³ first called the attention of the medical profession to it in a paper read before the Faculty of Medicine of Paris in 1806 It was he who used the term "melanotic" to depict one characteristic of the lesions—their color In 1820 Norris⁴ of Stourbridge, England, reported the history of a patient whose course, during life and postmortem findings, was characteristic of melanosis, though he referred to the case as one of "fungoid disease" The name *melanoma* was first used by Carswell,⁵ who read a paper with Cullen before the Medico-chirurgical Society of Edinburgh in 1833 and cited two cases

In 1858 in a treatise on melanotic cancer Pemberton⁶ described accurately the appearance of primary lesions in the skin, lower jaw, testicle, vagina and rectum, and secondary implants in the liver and other organs He presented 25 cases, including one in which a groin dissection was performed, and suggested removal of the "integument involved and the fascia of the muscle under it" He also recommended treatment with caustic, by itself or in conjunction with surgery Paget⁷ in 1865 reported 25 cases of melanoid cancer, in 18 of which the primary lesion was removed surgically Five of the 18 survived for more than four years He described three characteristics of the disease (1) the color of the lesions due to pigment formation, (2) the proneness of the tumors to grow in or beneath pigmented moles, and (3) the multiplicity of secondary melanoid formations

In 1907 Handley⁸ demonstrated the spread of melanotic cells along lymphatics and in fascial planes, and in 1908 Pringle⁹ first advocated the block dissection of tumor, lymphatics and regional glands which is recognized today as the treatment of choice

ORIGIN OF CELLS

The mystery of the origin of nevus cells has never been completely solved Three main theories have been held by different authors

1 Broders and MacCarty¹⁰ have maintained that malignant melanotic tumors are due to migratory hyperplasia of the basal (germinative) layer of the skin, cells of this layer invading the subcutaneous tissues and distant organs

2 Acton,¹¹ in studies on reptiles, concluded that in lower animals the melanoblasts form a primitive pigment sheet under the skin in close relation-

* Read before the American Surgical Association St Louis, Mo, April 20, 1949

ship to the angioblasts of the cutaneous respiratory capillaries. Whenever any surface downgrowth of the epiblast occurs it carries before it a portion of the primitive pigment vascular sheet, explaining the pigmented pia arachnoid of amphibians. Two types of cells are involved in melanotic tumors, melanoblasts, giving rise to melanosarcoma, and angioblasts (which, with melanoblasts, form benign moles) giving rise to malignant endotheliomas.

3. Spencer,¹² in studies on the tree frog, demonstrated that melanin pigmented cells are first developed around the neural tube for protection of the central nervous system, but later spread into the epidermis and deeper layers, and take part in the origin of melanotic tumors. Dawson,¹³ in 1929 presented histological evidence in favor of the epithelial origin of melanomas, supporting this theory by drawings of microscopic sections to show evolution of the melanoma cells from the deeper layers of the stratified epithelium. Horwitz¹⁴ in 1928 also supported this theory.

METHODS OF TREATMENT

Malignant melanomas arise in a great majority of instances from previously existing apparently benign pigmented or non-pigmented nevi. Driver and MacVicar¹⁵ found that 80 per cent of their cases gave a history of previously existing pigmented lesions. That trauma is an important cause of the malignant transformation of benign moles has been amply shown by the results of their study indicating that a history of injury preceded the transition of benign to malignant lesions was present in 58.3 per cent of cases. The cause of the transformation is not known. Ewing¹⁶ believed that if recurrence occurred following the excision of a mole, the lesion was malignant from the beginning. The Cohnheim¹⁷ theory supposed that pigmented moles harbor "sleepers" which on irritation become actively growing malignant cells.

Since most individuals have from 20 to hundreds of pigmented moles there has been considerable confusion on the part of the average physician concerning the treatment of such benign lesions. It is undoubtedly true, as Driver and MacVicar and Tod¹⁸ have pointed out, that inadequate or incomplete treatment of benign melanomata by physicians has resulted in the onset of malignant changes and in the development of malignant melanomata. A solution of the multiple mole problem has been suggested by various authors (Blair,¹⁹ Bloodgood,²⁰ Brown and Byars,²¹ Tod, Webster and Stevenson²²). Brown, flat moles and hairy moles seldom become malignant. Bloodgood reported the wide removal of 300 benign moles without complication or recurrence. Black lesions, especially if raised, which have appeared during life and are situated in areas of the body subjected to trauma should be removed by scalpel excision, leaving a surrounding margin of at least half an inch of normal skin and taking some subcutaneous tissue. Lesions showing evidence of growth, increase in vascularity or change in color should be removed widely, often with skin grafting. Blades²³ has stressed the importance of block excision of the chest wall in melanomas occurring on the chest. Pathological study of all lesions is imperative.



FIG 1

FIG 2

FIG 1—Malignant melanoma of the skin of the lower leg, showing local invasion (Courtesy Dr Walter Maddock)

FIG 2—Malignant melanoma of the chest wall, recurring in scar of previous excision (Courtesy U S Army Institute of Pathology)

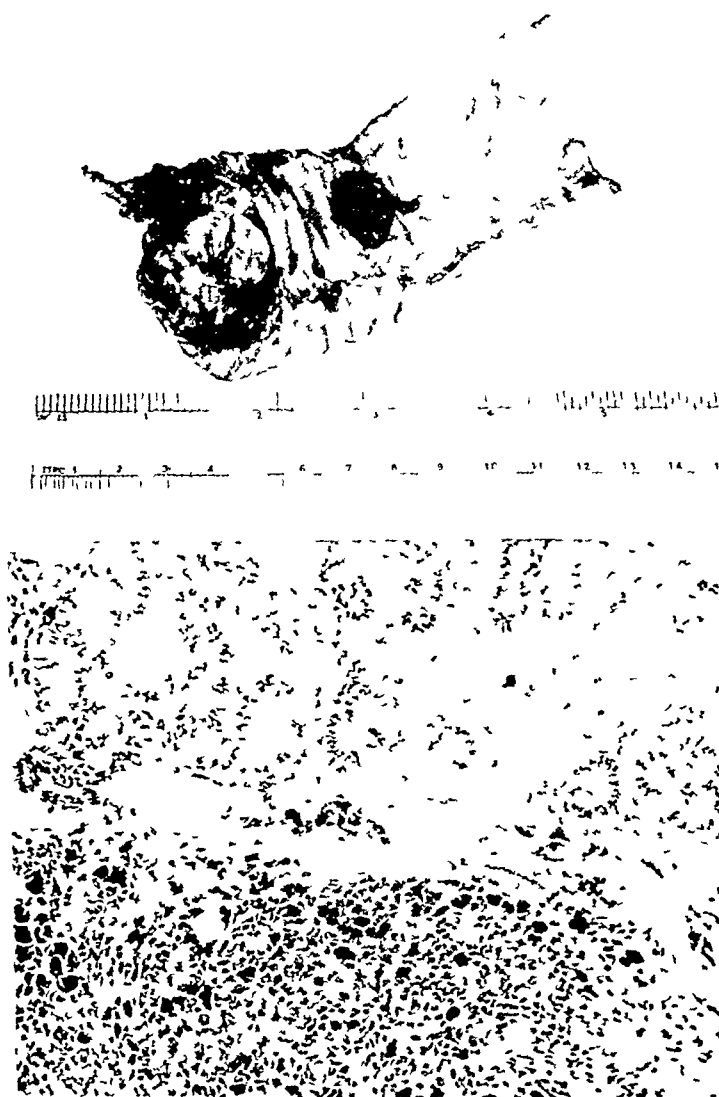


FIG 3—Hematogenous metastasis of malignant melanoma in the right hemisphere (Courtesy U S Army Institute of Pathology)

MALIGNANT MELANOMA

Once a melanoma has become malignant it may take one of three courses as outlined by Blair ¹⁹ It may grow locally, invading the surrounding skin and subcutaneous tissues (Figs 1, 2) It may be disseminated to distant parts, carried by the blood stream to lungs, liver, brain (Fig 3) or even intestine

A



B

FIG 4—Hematogenous metastasis of malignant melanoma in the intestinal wall (Courtesy U S Army Institute of Pathology)

(Fig 4) It may metastasize by way of lymphatic channels to the nearest regional nodes Local spread of the first type can sometimes be prevented by wide excision with skin grafting Metastasis by way of the blood stream cannot be controlled and accounts for many treatment failures It is in lymphatic metastasis to regional nodes that by early radical treatment our greatest hope of cure lies

In 1907 Handley demonstrated graphically the lymphatic spread of malignant melanomas. In a patient who had died of generalized melanosis following the metastasis of a melanoma of the heel to lymph nodes in the groin he removed a strip of skin 17 cm long from the thigh, with subcutaneous tissue and deep fascia for microscopic study. He was able to demonstrate that permeation by malignant cells takes place in a centrifugal direction from the lymphatic channels involved, extending much farther in the deep fascia than in the skin, subcutaneous tissue or muscle. In the following year Pringle described the method of nodal dissection for malignant melanoma which has not been improved upon during the past 40 years. To quote him, "a radical extirpation of the disease will most certainly be ensured by excision of the tumour with a good zone of healthy skin around it and a somewhat larger zone of the underlying subcutaneous tissue and of the deep fascia, with a broad strip of subcutaneous fascia up to and including the nearest anatomical group of glands at least, and all that is removed should be in one continuous strip as far as possible."

Occasionally, following radical dissections of this type, Pack²⁴ found that melanoma cells in lymphatic transit recurred in the wound. He has therefore recommended removal of the original lesion, followed by node dissection with removal of a strip of fascia as described by Pringle one or two weeks later if gross evidence of metastasis is present. If the nodal dissection is regarded as prophylactic, he believes it should be performed six weeks after resection of the original lesion. He reported that two thirds of the cases in which prophylactic nodal dissection was performed, without palpable nodular enlargement showed minute foci of metastasis in the nodes removed.

DeCholnoky²⁵ has summarized the results of treatment by various authors as follows:

Summary of 5 Year Arrests						
Author	Number Cases	Location	Therapy	Cases	Time	Percent 5 Year Arrests
Adair ²⁶	70	Head body extrem	Surgery	23	5 yrs	33
Affleck ²⁷	200	Head body extrem	Surgery	20	5 yrs	11.1
Bloodgood ²⁸	200	Head body extrem	Surgery	1	5 yrs	0.1
Daland Holmes ²⁹	82	Eye head body	Surgery	15	5 yrs	18.3
deCholnoky ²⁵	26	Eye head extrem	Surgery	11	5 yrs	42.3
				5	10 yrs	19.2
Gleave ²⁹	18	Eye	Surgery	9	5 yrs	50
Hirtze ³⁰	54	Head body extrem	Surgery	15	5 yrs	27
			and xray	5	13 yrs	9.2
Meland ³¹	50	Head body extrem	Surgery	9	5 yrs	18
Scharnagel ³²	70	Head body extrem	Electro surg and xray	27	5 yrs	39
Scott ³³	29	Head body extrem	Cautery	11	5 yrs	37.9
Average per cent of 5 year arrests						19.2%

Unfortunately most of these writers did not state whether or not lymph node dissections were carried out, and if so whether or not metastatic foci were found in the nodes removed.

MALIGNANT MELANOMA

CLINICAL MATERIAL

Forty cases of malignant melanoma were treated by surgical extirpation and radical nodal dissection at Walter Reed General Hospital from 1942 to 1946 inclusive. In most instances the melanoma had been removed elsewhere, often at an overseas installation, the patient being transferred to this hospital because of a pathological finding of malignant growth in the lesion. Except in a few far advanced cases treatment consisted in review of the transfer slide if available, followed by radical resection of the lymph nodes draining the area involved. The nodes were resected, whether or not they were palpably enlarged. In many instances the original scar was excised and a strip of skin and fascia between it and the lymph nodes removed en bloc.

Nine of the 40 cases were regarded as far advanced, evidenced by large, fixed, palpable lymph nodes, or distant metastases. Only one of these nine cases lived for more than a few months after operation. In three of the nine, because of the degree of fixation of the involved nodes or because of distant metastases, biopsies only were performed.

TABLE I.—*Radical Resection for Malignant Melanoma*

	Total Cases		Alive 1-3 yrs	Alive 4-6 yrs	Total Alive
	Number Cases	Proved Gland Metastases			
Regional gland enlargement	25	23 92%	3	0	12%
No regional gland enlargement	12	7 58%	9	2	88%
Gland enlargement not stated	3	1 33%	2	0	66%
Total	40	31	14	2	40%

All cases were divided into two groups, depending upon the presence or absence of palpable lymph nodes. There were 25 cases in which glandular enlargement was present on admission, 12 in which it was absent and three in which records were incomplete. Among the 12 cases in which no palpable adenopathy was present at the time of the lymph node resection 7, or 58 per cent, showed pathological evidence of metastasis in the nodes removed. All of these seven patients are now alive without evidence of further metastasis or recurrence for periods varying from one to six years since operation. Of five patients without palpable adenopathy or pathological evidence of metastasis in the nodes removed one died of distant metastases four months after operation. The remaining four patients are alive and well for periods varying from one to three years since resection. Only two of 25 patients in whom nodular enlargement was present at time of operation failed to show pathological evidence of metastasis in the nodes removed. One of these patients is alive and well two years and nine months after operation, one has shown roentgenographic evidence of a metastatic lung tumor two years and six months after resection. Of the remaining 23 patients with palpable adenopathy and pathological evidence of metastasis, 20 are dead, 18 having died in less than two

years after operation One is alive with metastases one year after operation, two have been alive and well for between two and three years

The following histories are presented to illustrate the types of cases encountered in this study

Case 1—A 35-year-old male who had had a 1 cm black, flat mole on the anterior aspect of his thigh all his life first noticed bleeding from it after crawling on his abdomen in army training in August, 1942 On January 21, 1943, the nevus was excised surgically Pathological diagnosis was malignant melanoma He was transferred to Walter Reed General Hospital on February 17, 1943 Examination on admission revealed the scar to be healed No inguinal adenopathy was present On February 26, 1943, a wide excision of the old scar was performed down to and including the deep fascia, and the defect covered by an immediate split thickness graft On April 22, 1943, a block dissection of inguinal and iliac lymph nodes was performed Pathological examination showed a nodule of metastatic melanoma in one of the inguinal glands removed In September, 1948, this patient was well without evidence of recurrence

TABLE II—*Radical Resection for Malignant Melanoma Cases with Proved Regional Gland Metastases*

	Number Cases	Alive 1-3 yrs	Alive 4-6 yrs	Total Alive
Regional gland enlargement	23	2	0	8%
No regional gland enlargement	7	5	2	100%
Gland enlargement not stated	1	0	0	0%
Total	31	7	2	29%

Case 2—A 28-year-old male had had a small bluish colored nevus below the angle of his right mandible for as long as he could remember In mid-April, 1945, he suddenly developed a painless lump about the size of a marble under the pigmented nevus On May 23, 1945, the tumor was removed It was darkly pigmented and was closely adherent to the capsule of the parotid gland, from which it was separated with difficulty Microscopic diagnosis was malignant melanoma, metastatic to lymph node, complete excision doubtful He was transferred to Walter Reed General Hospital Examination revealed a 6 cm incision in front of the lower lobe of the right ear with a non-tender blackish area the size of a bean 2 cm anterior to its lower end A few posterior cervical lymph nodes were palpable on the right side of the neck On July 26, 1945, a right radical neck dissection was performed with extirpation of the right parotid gland Pathological examination revealed metastatic melanoma in three lymph nodes removed from the neck and also in a lymph node imbedded in the parotid A letter from the patient dated August 26, 1947, stated that he was well but that new nodes had appeared in the left supraclavicular region

Case 3—A 38-year-old man first noticed a small dark spot on the skin over the crease of his right 4th metacarpophalangeal joint in June, 1945 In November, 1945, it began to increase in size rapidly until it reached 2 cm in diameter, and at the same time lost its pigment and became more or less flesh colored The lesion was excised with cutting cautery A pathological diagnosis of malignant melanoma was made On admission to Walter Reed General Hospital on February 15, 1946, examination revealed no axillary gland enlargement On March 13, 1946, a radical amputation of the left 4th finger was performed On March 28, 1946, a radical left axillary node dissection was carried out A pathological diagnosis of amelanotic melanoma, malignant, of the left hand was made and metastatic melanoma in eight of 15 axillary nodes removed He remained well thereafter until January, 1947, when a small wart-like nodule was found on the left

side of his neck This was removed and was reported to be malignant melanoma, possibly metastatic On January 8, 1947, a complete radical left neck dissection was performed Metastatic melanoma, amelanotic, was found in four of six glands removed It was learned indirectly that this man was well in August, 1948, although no details of his condition were available

Case 4—A 30-year-old white male had had a black, smooth mole on the outer aspect of his left upper arm all his life Because of gradual increase in size and vascularity it was removed on August 9, 1944 Pathological examination revealed malignant melanoma He was immediately transferred to Walter Reed Hospital Examination on admission showed a well healed scar and no adenopathy On August 22, 1944, a radical left axillary dissection was performed Early metastasis was found in one of the nodes removed A letter received from this patient dated August 17, 1948, stated that he was well, symptom free and showed no evidence of recurrence

Case 5—A 26-year-old man reported on sick call because of the beginning enlargement of a pigmented mole on the left side of his neck behind the sternomastoid muscle The mole was removed, leaving a wide border of normal skin around it Microscopic examination was reported to show evidence of malignancy He was transferred to Walter Reed Hospital Examination on admission was non-contributory No nodes were palpable in the neck On September 15, 1947, a block dissection of the left neck nodes was performed Melanotic metastases were found in the nodes removed Two weeks later enlarged left axillary nodes were palpated A block dissection of the axilla was performed The nodes removed showed no evidence of tumor In March, 1948, this patient was reported to be alive and well

Case 6—A 29-year-old white male noticed the appearance of a dark brown mole one half inch in diameter on his left chest wall during the summer of 1944 In August, 1944, the mole was removed surgically and was found to show evidence of malignancy on microscopic section On transfer to Walter Reed General Hospital no adenopathy was detectable clinically, but on October 13, 1944, a left axillary gland dissection was performed Examination of the tissue removed showed metastatic melanoma in one of nine nodes A card received from this patient dated August 25, 1947, stated that he was well without evidence of recurrence

Case 7—A 35-year-old white man had had a dark brown mole three-fourths of an inch in diameter on the anterior aspect of his right thigh all his life In November, 1943, it began to enlarge in size In January, 1944, the mole was removed Lymph nodes at this time were not enlarged Pathological report of the lesion removed was that of malignant melanoma In September, 1944, some enlargement of the right inguinal lymph nodes was noted A radical resection of the right groin and iliac nodes was performed Microscopic study of the nodes removed showed the presence of metastatic melanoma In a letter dated August 9, 1948, he stated that there had been no evidence of recurrence of the melanoma or of any nodular enlargement

Case 8—A 35-year-old male had had a pigmented mole on the center of his back since his earliest recollection In November, 1945, because of increased vascularity of the lesion, it was removed surgically and was reported to be cancerous by pathological section No lymphadenopathy was present, but in January, 1946, a right axillary node dissection was carried out and in May, 1946, a similar resection on the left side Metastatic melanoma was found in the left axillary nodes A letter received from him on July 23, 1947, stated that he was well without evidence of recurrence

SUMMARY

Forty cases of malignant melanoma have been treated by surgical excision and regional node resection In 25 cases nodular enlargement was present at

time of operation In 23 of these, metastases were present in the nodes removed Only two of these 23 cases are now alive and well In twelve cases no palpable adenopathy was present at time of operation Nodular metastases were present in seven, or 58 per cent of the twelve cases All seven are now alive and well for one to six years after radical block dissection of the regional glands involved

Comparison of results in these two groups of cases demonstrated conclusively the importance of early radical resection of regional lymph nodes, whether or not they are enlarged, whenever a diagnosis of malignant melanoma is made To wait for clinical enlargement of regional nodes before undertaking their block dissection is to ensure a high percentage of recurrences Eighty per cent of patients in this series who had palpably enlarged nodes at time of operation are now dead or show evidence of recurrence All of the patients without such preoperative nodular enlargement are now alive and well

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DISCUSSION —DR ROBERT H KENNEDY, New York City Dr McCune has brought up an important subject I find, in New York at least, that there is still considerable feeling among the general practitioners, and unfortunately among a certain number of general surgeons, that with the diagnosis of melanoma (or the probable diagnosis) the patient is better off if left alone We have to overcome that idea

I concur with Dr McCune entirely that there is much to be gained by doing what I like to call a "prophylactic" lymph node dissection, although all too commonly what one thinks is a prophylactic dissection is proved by the pathologist to show one node with a few melanotic cells, or even a number of small involved nodes which were not large enough for anyone to palpate

There is a region where I do not believe in doing a lymph node dissection We see quite a few cases where there is involvement of the region either about the umbilicus or the middle of the back In these we have seen instances in which the metastases have gone to either axilla or either groin Therefore I have felt that I had to wait until I had some evidence of metastases rather than doing four prophylactic node dissections which seemed more than I had a right to put the patient through

One of the great problems in melanoma is the variation in malignancy The individual life history shows more variation than in most types of cancer For example, in 1927 a woman presented herself at the age of 49 who had had dental treatment fourteen years previously, in which her right lip was pinched, and ever since then she had had a black spot This started to grow about two months before admission

Examination showed a 3 cm ulcerated area on the mucous membrane of the mouth within the cheek There was also a black area on the upper lip, the lower lip, extending down into the sulcus between the cheek and jaw and extending up between three of the teeth

My first thought was that there was no use in removing this, because of the rapid growth in only two months But my attendant, the late Dr Franz Torek, of this Association, said, "Well, death from ulceration in the mouth is a horrible thing I would take it out"

So I planned carefully how I would close the area after making an excision of about one-third of the upper lip and one-quarter of the lower lip and carrying the complete cheek excision back beyond the anterior border of the masseter muscle As I was ready to start my closure, Dr Torek happened to come into the operating room and said, "That's fine, I wouldn't do anything more" It upset me considerably to leave

this area about three inches in diameter wide open into the mouth cavity when we were trying to relieve her discomfort. Over a period of about two months this closed in quite well.

The lesion showed all of the characteristics of malignant melanoma, including even that portion of the mucous membrane between the teeth and passing to the inside of the alveolar margin. The entire black area seemed to be melano-carcinoma.

The only further operation was a small flap turned to make a new angle of the mouth. Otherwise, that entire defect, which at one time was over three inches in diameter, closed. At that time we did not do a lymph node dissection because we all agreed we had been lucky and we expected the local lesion to recur.

At about two and one-half years she developed a number of nodes in the neck, and I felt that inasmuch as she had lived for this time without local recurrence we ought to do more. I started a complete right lymph node dissection, and when I reached the supraclavicular region I was tired of finding multiple perfectly black nodes, so I did not continue to the clavicle. By pathologic examination the only involved node was one in the submaxillary region, about 2 cm in diameter, otherwise the nodes showed simply black foreign body pigment of some type.

I have seen her at intervals of one year after the first five years. She is now bringing up her grandchildren. It has been 22 years since excision of the original lesion, and almost 20 years since the lymph node metastasis was removed. It was worth while to do the work, but in spite of the highly malignant appearance of the cells in the slides this must really have been a melanoma of low grade malignancy.

DR GRANTLEY W TAYLOR, Boston. We are very much impressed with Dr McCune's conscientious survey of his materials. Talking with Dr White about it, we wish some of the cases might have been followed a little longer. That is something that the future holds.

We did a careful study of our material at the State Cancer Hospital and at the Massachusetts General, studying about 176 cases. First of all, I think Handley's conclusion that the spread by way of permeation is not invariably or usually a true state of affairs. If that were so we would never cure anybody by a discontinuous operation, that is, removal of the primary and the regional nodes as two separate procedures, leaving the intervening lymphatics.

I think the appearance of permeation arrives when the nodes are so blocked that the lymphatic flow is delayed or there is some stasis, and that permits the propagating thrombus to emerge from the primary focus of disease and spread itself.

The factors resulting in failure after a dissection are worth while analyzing. Dr McCune touched on the fact that blood-borne metastasis is common, and although not the earliest manifestation as a rule, it is all too common later. We found, in analyzing our failures, that a large number of them were due to failure to control the primary disease. A recrudescence of malignant neoplasm at the primary focus after the dissection has been carried out, of course, vitiates that dissection. As long as there is any lymphatic drainage it must seek collateral channels, and often the dissection carried before eradication of local disease insists that collateral drainage pass by a very bizarre route, so that other areas of metastasis may appear which would not have supervened.

A very interesting recent example is that of a case of a woman with a lesion on her right ankle. The right groin dissection was carried out, and it was positive. A recrudescence occurred at the right ankle and the next metastasis appeared in the left groin. They must have crossed lymphatic channels going across the perineum and external genitalia to reach the opposite groin.

Dr Kennedy referred to the difficulty of deciding what area to dissect when the lesion is in the midline or is somewhere near the belt level, where you can't be sure in which directions lymphatic drainage goes. At the present time we have a young

man at the Massachusetts General Hospital who had a lesion over his fourth lumbar vertebra, with metastases to both axilla, and he has just had the second groin dissection carried out, so he has had dissection in all four areas

In our study we found one person who, in addition, had a supraclavicular metastasis, so he had five of his possible radical dissections carried out

The principal problem is to be sure that the primary disease is controlled, and therefore we invariably defer our regional dissection, if we can, until at least (we will say) two or three weeks have elapsed, until we have some confidence, from the examination of the pathological material in the local area, that probable local extirpation has been achieved

It is very hard to train house officers to carry out the wideness of the dissection which you think is desirable. You can say "a wide excision," but they are inclined to treat these like more benign lesions of epidermoid carcinoma and basal cell carcinoma, and quite often there is some residual local pathology

DR KELLOGG SPEED, Chicago Mr President and members, I wish to say something about metastases, illustrating by one patient, and also something about the melanotic features of these tumors

I had consult me, a few months ago, a factory superintendent 46 years of age who had bumped his knee, it had become swollen and painful. There was some enlargement, without any adenopathy in the groin or in any of the lymphatics

(Slide) This film showed a defect in the head of the tibia, with excavation and lytic absorption, which we felt was probably a secondary tumor. He was very carefully examined by several consultants, including an ophthalmologist, and we could not find any trace or origin of the nature of the tumor. He did yield to a biopsy and a black, melanotic, soft tumor was found in the head of the tibia

(Slide) Following discovery of this melanoma in the bone, the limb was amputated with his consent, though we knew the growth was secondary. Before that amputation he had another complete physical re-examination and all we could find were one or two small black skin tumors in the lumbar region

I call your attention to this point at the end of the femur where the amputation was performed. There is black tissue, although the main tumor is in the tibia, as you can see. When the leg was amputated there wasn't the slightest sign of discoloration around the area of the femur, and it was perfectly clean-looking normal bone

(Slide) This microscopic section shows the invasion of the tibial head by the typical melanotic malignant tumor

(Slide) This section shows the involvement of the skin tumor, in the lumbar region, which was removed at the time of the amputation. It was not as large as my little finger nail

(Slide) About four months later he returned with an exostosis developing at the end of the femur. This interfered with the wearing of his prosthesis, and therefore we removed it

(Slide) Upon removing it we found that it had an extension of bony nature, but it was perfectly normal in color, that is, normal yellowish bone. There was no discoloration whatsoever

Five or six days later, as his tumor lay in the laboratory in a receptacle, the excised mass of exostosis became darker and darker, and finally got very black. The pathologist, in the gross description of it, said it was probably a melanotic metastasis. The sections of that later on showed absolutely no cellular ingrowth of tumor into that exostosis. There had developed while lying in the laboratory simply a deposit of a melanotic pigment around the end of it

The point I wish to make is that there is melanotic pigment in the blood which has never been examined or tested for, but it has been found in the urine, and if the urine of some of these patients is taken and exposed to light, and oxidized, there

will develop a black tinge or evidence of melanin from the blood as excreted by the urine which may be of help in determining whether a tumor is metastasizing and whether it is malignant. All patients with melanotic tumors, of whatever size or situation, should therefore be studied for the presence or absence of melanin in the blood serum or urine with hope of determining the prognosis in each case where the findings are positive. This test may give the first evidence of metastases in the making or already present.

DR RALPH F BOWERS, Memphis, Tenn. We were stimulated at Walter Reed by Dr McCune's work regarding two things, that melanoma is not the dangerous tumor that we all believe it to be, and that it does not necessarily deserve the existing defeatism, when compared to other dangerous malignant conditions.

I also became convinced at Kennedy Hospital, where we have had 34 of these lesions in less than three years, that there is question whether or not surgery, as we employ it today, is actually effective in the disease and whether or not the reported longevity is due to the surgery or the natural course of the tumor.

For instance, we have one patient who lived seven years without any treatment. We have had two cases with inadequate dissection or removal of melanoma from the shoulder region, who came to us four years later with metastases. Both of those patients survived more than five years, yet both had inadequate local excisions as manifested by the appearance of melanotic tissue in the scar shortly after the original excisions.

Along this line, Dr Taylor brought out a few points that led us to the radical approach we are now using, and we have done it in six cases. The lymphatics are involved, and in the Handley procedure, we have shown that lymphatics, deep to the fascia of the muscle, are often involved, which certainly suggests that resection in continuity is not always an adequate operation.

We became convinced that one must not touch the local lesion except for the necessary biopsy, and must not manipulate or cut across lymphatic channels or its first main nodal barrier, and therefore we devised a more radical procedure in the treatment of melanoma, particularly in those cases below the umbilicus, which all of us know to be prompt killers.

We have done six cases, two of the arm and four of the leg—quarterectomy—by that I mean intrascapulothoracic amputation for the arm cases and hemipelvectomy for the leg cases. The hemipelvectomy that we employ is a little different from that described by Morton. The anterior skin incision is made in a semicircular fashion, approximately three inches above the inguinal ligament, in order that we will in no way interrupt the lymphatic channels or cut into the femoral, inguinal, or iliac glands below the level of the hypogastric artery.

Our premise states that to offer anything surgical to melanoma, we must eradicate the primary lesion, the lymphatic channels, and the main nodal barrier in one sweep, preferably without touching any of these structures during the procedure.

Our cases have not gone for a long period of time postoperatively. Frankly, we did not relish the idea of performing quarterectomy without obvious lymphatic nodal involvement. But we performed two lower quarterectomies when we could not clinically discern the lymphatic involvement. Both of those cases had involvement of a single node in the femoral group.

It is interesting to note when one incises the skin, subcutaneous tissue, and muscles above the inguinal ligament to the level of the hypogastric artery, that the iliac glands are free of disease even with demonstrable involvement in the femoral node—at least such was the situation in our leg cases. We know this is mutilating, but I think if you gentlemen were forced to view 34 cases of melanoma in a period of three years, and saw the rate of death, you would appreciate our belief that we are not too far wrong in urging these more radical procedures.

DR MIMS GAGE, New Orleans That malignant melanoma should be treated, just as all carcinomas, by wide excision of the primary lesion and radical removal of the contiguous and regional lymph nodes has been ably stated by Dr McCune I am in complete agreement with the method he describes

There are two points I would like to emphasize Firstly, many surgeons and dermatologists treat potential malignant melanomas by coagulation This method of treatment should be condemned because of the poor results, as shown by Amadon in 1933, and this has also been my personal experience Most of the hopeless lesions which I have seen have been previously treated by the cautery method, regional and extensive metastasis being present without any evidence of local activity in the scar at the site of removal of the primary lesion However, small black areas a millimeter or so in size can be found in the scar

The second point is the late recurrence of distant metastasis without local activity Three patients recently came to the Ochsner Clinic with a history of having had a melanoma removed One patient had his eye removed twenty years before coming to the Clinic, he had a metastatic nodule in the subcutaneous tissue of the abdominal wall The second patient had a pigmented mole on his right leg above the ankle destroyed by the electric needle There was some pigment in the scar, about 7.5 cm distal to the scar, and 18 cm proximal to the scar were cutaneous nodules which proved to be carcinomatous

The third patient had a melanotic mole in the lumbar region over the spine destroyed by active cautery ten years previously There were some small areas of black pigment in the scar but no local activity However, there was a larger mass in the right inguinal region This demonstrates what happens when the primary lesions are destroyed by the method of electrical or actual cauterization This observation is general but unfortunately is never heeded, and both the doctor and the patient become inmedicable

I think it is difficult to formulate statistical reports regarding longevity following surgical treatment of malignant melanomas because of the late metastasis—five to 25 years after the primary operation However, I must admit that most patients have been inadequately treated from a surgical standpoint I believe that if all patients are treated by radical excision of the primary lesion combined with lymphatic ablation, recurrences will be negligible

Malignant melanoma will always pose a most serious problem because of its malignant peculiarities If the lesion demonstrates carcinomatous characteristics, the lymphatics are involved first and therefore the prognosis as regards radical surgical measures is better However, if the lesion manifests sarcomatous characteristics, it metastasizes first via the blood stream and secondarily via the lymphatics Therefore, there is widespread interval metastasis, which prevents radical excision of the lesion It is in this latter group that the mortality is high and treatment is almost completely hopeless

DR WILLIAM S McCUNE, Washington, D C I wish to thank those who have discussed this paper and added so many helpful comments

In regard to the variation of malignancy in the different types of melanoma, it is quite true that such variation is great and we hope in the future to be able to correlate the clinical follow-up of these patients with a review of their pathological findings

Certainly it is true also, as Dr Gage has remarked, that often these tumors do not recur or metastasize for as long as 12 or even 20 years, and this makes our statistics difficult to evaluate However, we feel that since the statistics we have indicate that those patients with radical node resection fare better than those without, or than those in whom it is delayed, this procedure should be continued

We are convinced that all involved lymph nodes should be removed by block dissection unless or until multiple distant metastases make the tumor clearly incurable One patient with a melanoma on the anterior wall of the sternum had a bilateral

axillary gland resection, followed later by a radical neck dissection. Still later he developed an enlarged node on the opposite side of the neck, and at that point further surgical excisions were decided to be useless. He died about two years following the first operation.

Another of these patients was admitted following removal of a malignant melanoma of the hand. He had a typical Handley type of gland resection, but later developed a lesion in the skin of his neck which was diagnosed also as malignant melanoma. Whether it was a metastasis from the original lesion or another instance of the same type of tumor, we never knew. He had a radical neck dissection and he has now returned with multiple metastases.

I should like to say that in the work done at Walter Reed Dr. Bowers was a great inspiration to us. He convinced us of the wisdom of many of his radical methods of treatment.

DEVELOPMENT OF NEW METHODS FOR THE HISTOCHEMICAL DEMONSTRATION OF HYDROLYTIC INTRACELLULAR ENZYMES IN A PROGRAM OF CANCER RESEARCH*

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THE HISTOCHEMICAL ANALYSIS of the enzymatic content of normal and neoplastic tissues, as a basic approach to the cancer problem, has been the subject of considerable interest in the past decade. Further stimulus was afforded by the development of methods for the direct microscopic visualization of the sites of enzymatic activity in the tissues themselves. A number of methods for several enzyme systems have been proposed, and some of these have been used extensively.¹ In order for such methods to serve as useful tools in a variety of problems related to cancer and other medical disciplines, they must be convenient and simple to execute, they should offer clear microscopic delineation, and they should have some degree of specificity. Variation in the properties of the enzymes, such as the degree of activity or their concentration in tissues, their stability to heat and tissue fixatives, their pH optima, their solubility, and finally their hydrolytic behavior toward synthetic substrates which incorporate features for good pigment production, serve to increase the difficulties in developing means of demonstrating them.

One of the earliest methods for visualizing the sites of enzymatic activity was to utilize physiological substrates and develop pigments, where it was possible, with one of the hydrolytic products. An example of this is the method of Gomori² for alkaline phosphatase. In this case phosphoric esters of glycerol, glucose, adenosine and other substances may be used, and the phosphate produced by enzymatic hydrolysis is converted to an insoluble metal salt which may be visualized by conversion to either metallic silver or lead sulfide.

Another approach is to use a synthetic unnatural substrate, which contains a chromogenic moiety. After hydrolysis, this organic fragment of the substrate is converted to a colored pigment. An example of this is the method of Menten *et al*³ for alkaline phosphatase. In this case a phosphoric ester of beta naphthol

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(I) is converted by enzymatic hydrolysis to beta naphthol (IV) in the presence of a diazonium salt, which immediately couples to yield an insoluble colored azo dye at the site of enzymatic activity

The latter approach yielded a more sensitive and rapid method and appeared to offer promise of the development of methods for demonstrating enzyme systems which have hitherto been inaccessible, as well as for improving those for which methods were already in use. This approach thus formed the basis of the investigations to be presented below. Also included is a note on the outgrowth from this work of a rationale for new agents of possible chemotherapeutic value in cancer.

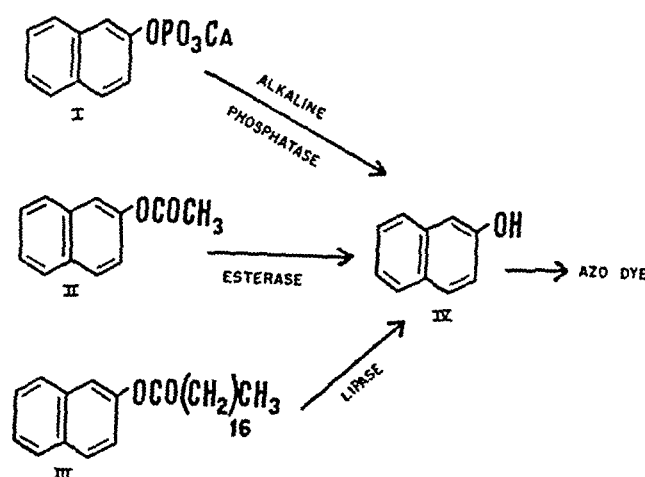


CHART I

ALKALINE PHOSPHATASE

The method of Menten *et al*³ for alkaline phosphatase which utilized calcium beta naphthyl phosphate (I) as substrate was made practicable by the preparation of a stabilized diazonium salt of alpha naphthylamine⁴. By this means, the method was reduced to the addition of two powders to a buffered solution into which the tissue sections were introduced for 20 minutes at 10 degrees C, by which time a satisfactory degree of staining of the section was obtained. The distribution of alkaline phosphatase in various normal tissues and tumors of humans was explored by this method⁴. Four significant findings may be pointed out: (a) Many of the arterioles of normal tissue, particularly brain, contained alkaline phosphatase, but vessels of similar size in neoplastic tissue were nearly devoid of this enzyme. (b) Several hypernephromas were found to contain variable amounts of alkaline phosphatase. In some the concentration and pattern of distribution of the enzyme closely resembled that found in the tubular epithelium of the kidney cortex. Adrenal cortex, on the other hand, contained very little alkaline phosphatase. These findings suggest that the cell of origin of these tumors was the tubular epithelium of kidney cortex. (c) Carcinomas of stomach were practically devoid of alkaline phosphatase, whereas, carcinomas of ovary contained a delicate pattern of the

enzyme similar to that of the ovarian stroma. This afforded a means of determining whether undifferentiated tumors of the ovary were carcinomas primary in that organ or metastatic from the gastrointestinal tract (Krukenberg)⁴ (d) Benign tumors of the human breast may or may not contain alkaline phosphatase in contrast to the regular absence of phosphatase in breast carcinoma

ACID PHOSPHATASE

Attempts to extend the procedure for alkaline phosphatase to acid phosphatase by merely changing the pH, met with failure. Although the phosphoric acid ester of beta naphthol is hydrolyzed readily by acid phosphatase, beta naphthol (IV) does not couple well with the diazonium salt at pH 4.8, whereas

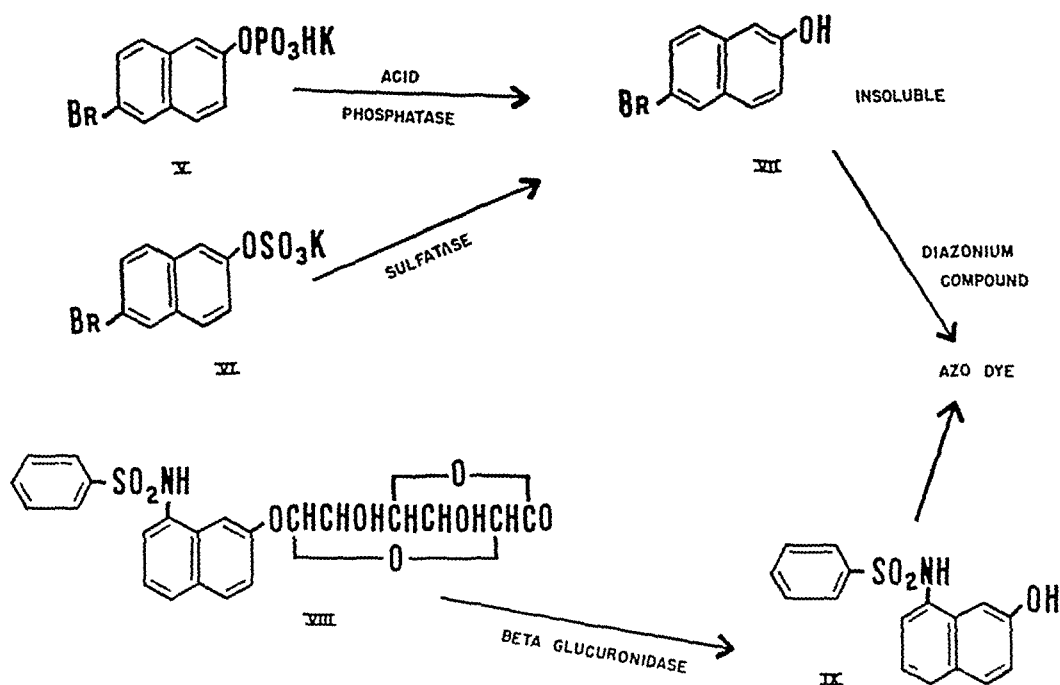


CHART II

alpha naphthol does. Acid phosphatase required longer incubation (one hour for prostate and 24 hours for other tissues) than alkaline phosphatase (20 minutes) and a higher temperature (room temperature) was required than for alkaline phosphatase (10 degrees C). Under these conditions the diazonium compound used for alkaline phosphatase decomposed extensively. Diazotized 1-amino-anthraquinone was found to be sufficiently stable under these conditions, and with calcium alpha naphthyl phosphate as a substrate, a method for acid phosphatase was provided⁵.

By using tartaric acid as an inhibitor⁵ it was possible to inhibit the cytoplasmic acid phosphatase of prostatic sections without altering the action of acid phosphatase of prostatic nuclei and of many other tissues. Evidence was thus afforded that prostatic cytoplasmic acid phosphatase and the phosphatase

of prostatic carcinoma differed from other varieties of acid phosphatase in the body

SULFATASE AND BETA GLUCURONIDASE

The sulphuric ester of beta naphthol and the beta glucuromide of beta naphthol (isolated from the urine of rabbits fed naphthol), were readily split by the respective hydrolytic enzymes. The alpha isomers were split poorly

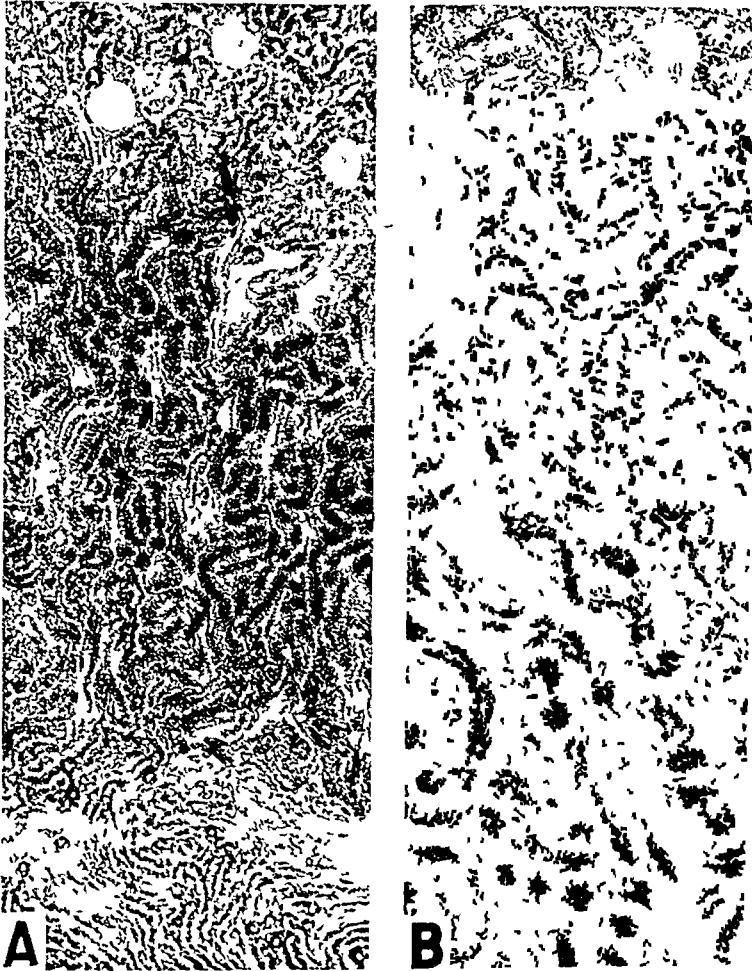


FIG 1—(A) Rat kidney. Sulfatase demonstrated by a blue azo dye. Enzymatic activity is present in varying amount throughout the nephron and in the excretory ducts (not shown). Fixed in formalin for two hours, and frozen sections incubated for 24 hours. Photographed through a red filter $\times 50$. (B) Same section, showing two patterns of distribution of sulfatase in tubular epithelium. The convoluted tubules are diffusely stained (top), whereas, the dye is concentrated at the luminal borders in loops of Henle. Photographed through a red filter $\times 114$.

However both enzymes have pH optima between 4.5 and 6 and, therefore, coupling with the diazonium salts did not proceed well enough for the development of good histochemical methods. The optimal temperatures were high and the time of incubation ran into many hours.

A new principle was, therefore, evolved. Because both the sulfate and glucuronide groups conferred considerable water solubility on the substrates, it seemed possible to use colorless substrates of significantly higher molecular weight, so that after enzymatic hydrolysis the phenolic material would be sufficiently insoluble (VII and IX) to remain fixed at the site of its production, thus eliminating the need for incubation in the presence of the diazonium salts. It was important to use colorless substrates because of the danger that

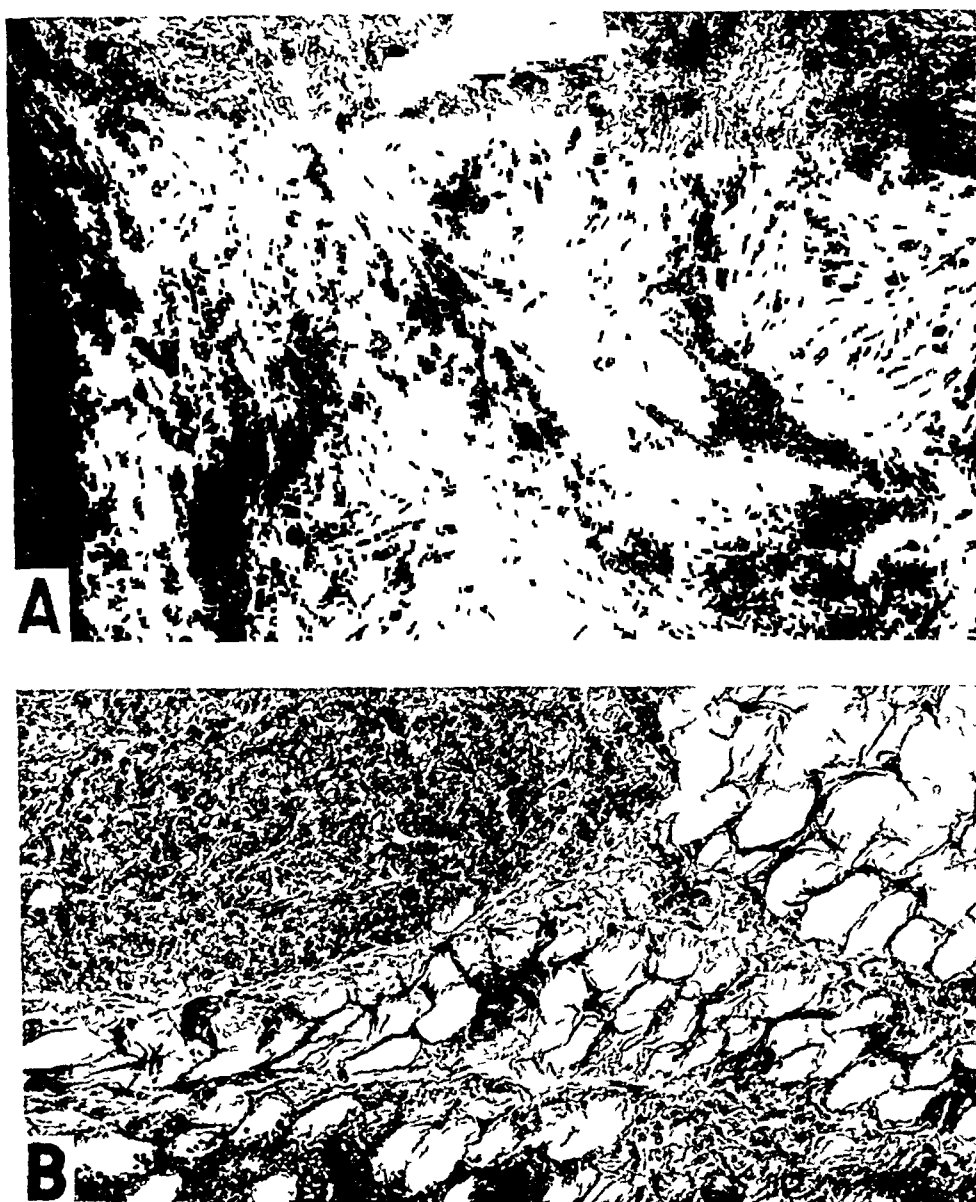


FIG. 2—(A) Human breast, scirrhus carcinoma. Glucuronidase demonstrated by a blue azo dye. Enzymatic activity in duct wall (left border of figure), blood vessel (top) and scattered collections of epithelial cells between the strands and whorls of fibrous tissue. Formalin fixed briefly and frozen sections incubated for 48 hours. Photographed through a green filter $\times 165$. (B) Human breast carcinoma. Acid phosphatase demonstrated by a blue azo dye formed after enzymatic hydrolysis of the phosphoric ester of 2-hydroxy-6-bromonaphthalene. Normal fat tissue and invading carcinoma show enzymatic activity. Fixed in acetone and embedded in paraffin. Incubated for 24 hours. Photographed through a green filter $\times 165$.

the acid groups (sulfate and glucuronide) would result in non-specific attachment to tissue protein. After a period of incubation sufficient to insure extensive enzymatic hydrolysis, the pH could be raised to that optimum for coupling, and then with an appropriate diazonium compound (tetrazotized diorthoanisidine) a blue pigment could be produced within one to two minutes in the cold. This procedure would insure a clear background to the tissue sections. The first substrates studied (prepared from 3-phenanthrol) were not hydrolyzed rapidly enough, nor was the phenanthrol sufficiently insoluble to insure a sharp picture. Satisfactory substrates for sulfatase and acid phosphatase

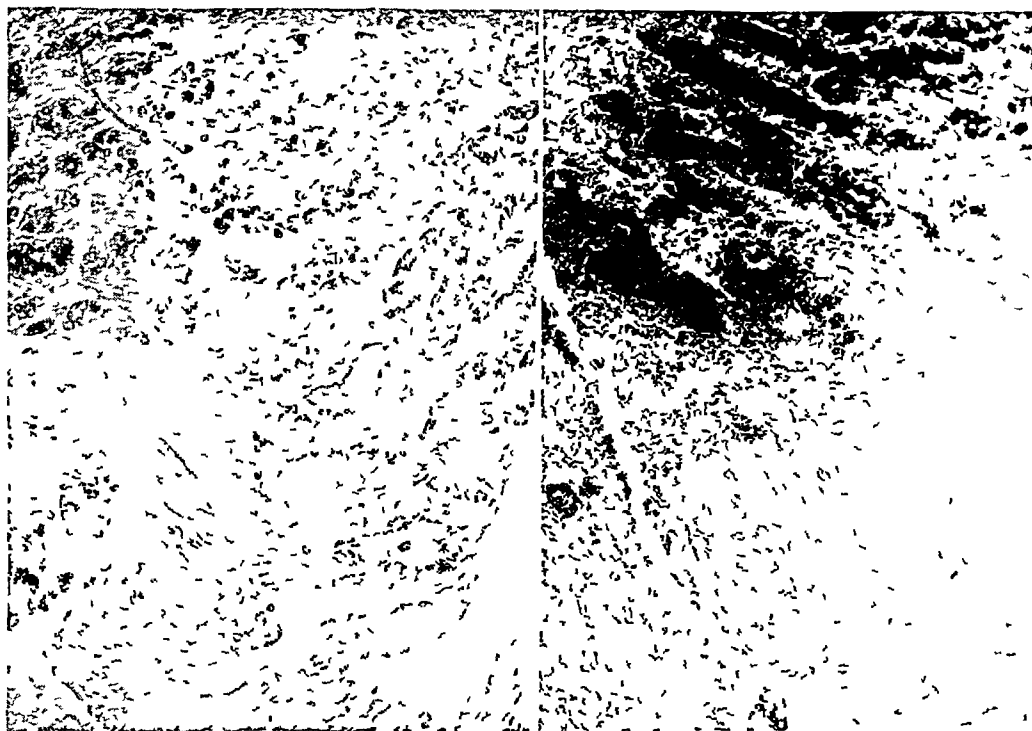


FIG 3

FIG 4

FIG 3—Human stomach, undifferentiated carcinoma. Acid phosphatase demonstrated by a blue azo dye. Acetone fixed and paraffin embedded. Incubated for 24 hours. Normal gastric mucosa (at top) and carcinoma (at bottom). All tissue contained acid phosphatase, but activity was most marked in normal glands and particularly in the parietal cells. Photographed through a green filter $\times 112$.

FIG 4—Human stomach, undifferentiated carcinoma, adjacent section to that in Fig 3. Esterase demonstrated by purplish red azo dye after 20 minutes incubation. Enzymatic activity seen only in the normal gastric glands located at the base of the mucosa. Glands near the surface epithelium were low in enzymatic activity. Parietal cells seen in upper right corner. Remnant of a gland containing esterase seen in carcinoma at lower left. The carcinoma cells were devoid of esterase. Photographed through a green filter $\times 112$.

was provided by the appropriate esters of 2-hydroxy-6-bromo naphthalene (VII). A satisfactory substrate for glucuronidase was eventually evolved from the glucuronide of 2-hydroxy-8-benzene sulfonamino-naphthalene (IX). The glucuronide of 2-hydroxy-8-amino-naphthalene was isolated from rabbit urine after feeding 2-hydroxy-8-naphthylamine and was converted to the sub-

strate (VIII) by treatment with benzene sulfonyl chloride. The methods for sulfatase,⁶ beta glucuronidase,⁷ as well as a new method for acid phosphatase,⁶ are now in process of being perfected. (See Figs 1, 2 and 3)

ESTERASE AND LIPASE

These are two distinct enzymes. In man pancreatic tissue contains both enzymes, while liver and kidney contain esterase almost exclusively. Serum normally contains esterase and no lipase (man) or traces of lipase (dog). The ideal substrates for lipase are glycerides of long chain fatty acids ($C_{16} - C_{18}$) and the ideal substrates for esterase are a variety of monocarboxylic acid esters of short chain fatty acids ($C_2 - C_4$). However, considerable overlapping occurs, and fats such as tributyrin are split by both enzymes. In an attempt to develop methods which would be specific for each, four substrates were studied. These were beta naphthyl acetate (II), beta naphthyl laurate (C_{12}) and beta naphthyl palmitate-stearate (III). The first two were hydrolyzed extensively by homogenates of liver, kidney, pancreas and by serum. The palmitate-stearate was hydrolyzed poorly by homogenates of liver and kidney or by serum, but was readily hydrolyzed by pancreatic mash. With the aid of inhibitors (arsenite for esterase and quinine for lipase) and an activator of lipase (taurocholate) it was shown that 90 per cent of the hydrolysis of the acetate by rat liver was due to esterase, and that 80 per cent of the hydrolysis of the laurate by rat pancreas was due to lipase.⁸

The acetate proved to be a satisfactory substrate for a histochemical method for non-specific esterase.⁹ An example is illustrated in Fig. 4. By inhibiting esterase activity the same substrate demonstrated lipase activity in pancreas. Other tissues did not have enough lipase activity to be demonstrable histochemically by this method.

The palmitate-stearate (III) and laurate could not be used for a histochemical method for lipase because of their great insolubility in water and inability to diffuse into tissue sections when made into a colloidal suspension. However, the colloidal suspension served as an excellent colorimetric method for measuring *lipase activity in serum*^{10, 11} and tissue homogenates. The azo dye produced on coupling with the liberated naphthol could be extracted from the serum with ethyl acetate and measured colorimetrically. Rises in the lipase activity of serum were demonstrated in dogs after injection of mecholyl and eserine.¹⁰ This method is rapid and sensitive to minute amounts of lipase, particularly when taurocholate is used as a specific activator of lipase. Using beta naphthyl laurate, 0.002 mg. of human pancreatic tissue (homogenate), added to 0.2 cc. of serum, could be identified by its lipase activity within five hours.

ACETYLCHOLINESTERASE

In seeking a suitable substrate for acetylcholinesterase, an attempt was made to incorporate essential features of the acetylcholine structure into an aromatic phenolic compound. The acetate of 8-hydroxy quinoline methyl chloride (X) appeared to satisfy the criteria, that is, it contained a quaternary

nitrogen and two carbon atoms away from this group an acetoxy group¹² The compound was hydrolyzed by fresh brain tissue in the cold, but unfortunately the compound hydrolyzed spontaneously, even in the cold, at pH 6.0 to a degree which mitigated against its use in a histochemical method. A more satisfactory substrate (XI), which satisfied the structural requirements, was provided by the acetate of 3-hydroxy-trimethyl-2-naphthyl ammonium iodide¹³ Spontaneous hydrolysis was not a serious problem, and the compound was readily hydrolyzed by fresh brain tissue.

RATIONALE FOR CHEMOTHERAPEUTIC AGENTS IN CANCER

Disubstituted phosphoric esters (XII) are being prepared from the naphthols and beta chloroethyl vesicants (sulfur and nitrogen mustards). If these products are less toxic than the mustards, the selective hydrolysis of such substrates by carcinoma rich in acid phosphatase (prostatic and gastric) might liberate mustards in sufficiently high concentration to destroy tumor cells. If,

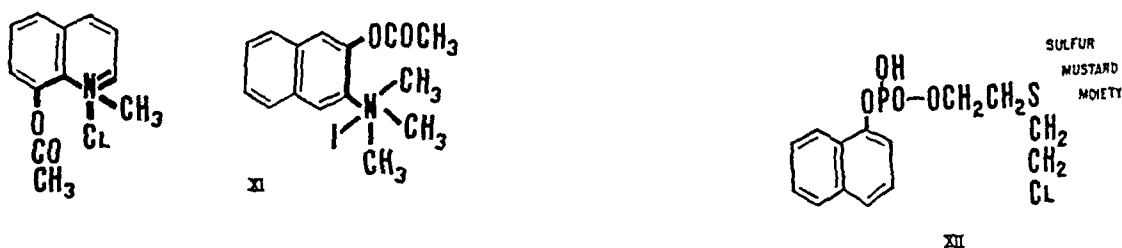


CHART III

however, the disubstituted phosphate containing a mustard moiety should prove to be more toxic than the split product, then use would be made of the fact that the beta naphthol derivative would be split by alkaline phosphatase. The widespread abundance of this enzyme in normal tissue would serve as a detoxification mechanism, and this means of detoxification would not be available to most carcinomas, which are practically devoid of alkaline phosphatase. In this way, greater specificity might be afforded mustard therapy than is possible at present. Disubstituted phosphate esters are indeed split by the phosphatases. The synthesis of the naphthyl mustard phosphate is in progress¹⁴ Similar use could be made of the finding of Gomori,¹⁵ that phosphamidase activity is high in carcinoma. The preparation of non-toxic phosphamide derivatives of the mustards is also in progress.

Acknowledgment is due Mr. Myron Milden and Miss Marie Mollomo for technical assistance, and Mr. Leo Goodman for the photomicrography.

SUMMARY

Utilizing the principle that enzymes are able to hydrolyze synthetic substrates which may be converted to insoluble colored pigments, histochemical methods for a variety of hydrolytic enzymes have been developed and others are in process of being perfected. Principles used in developing new methods are discussed.

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DISCUSSION—DR ARNOLD M SELIGMAN, Boston In the time allotted for discussion, I might mention one outgrowth of the work reported, which should be of particular interest to you

Utilizing the substrates which are hydrolyzed by lipase, naphthyl laurate or naphthyl stearate, it has been possible to develop a convenient colorimetric method for serum lipase This colorimetric method is more sensitive than the present titrametric methods, which use olive oil as substrate and which depend upon titration of the fatty acid produced by enzymatic hydrolysis Only 0.2 cc of serum is required for the determination, and incubation can be reduced from the usual 24-hour period to four to five hours This method should lend itself to routine use by clinical laboratories, and will serve as a useful adjunct to routine amylase determinations in the diagnosis of pancreatic disease and will be of particular value in the diagnosis of pancreatic carcinoma

SURGICAL TREATMENT OF CONGENITAL PULMONARY STENOSIS*

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INTRODUCTION

SHUNTING BLOOD to the lungs for the relief of cyanosis due to congenital pulmonary stenosis is at present an accepted surgical procedure. Blalock and Taussig¹ opened this field of surgery by anastomosing a systemic vessel to a pulmonary artery. Potts, Smith and Gibson² described a method of making a direct anastomosis between the aorta and a pulmonary artery. Obviously, the objective of each operation is the same. Subclavian-pulmonary or aortic-pulmonary anastomoses are actually makeshift operations which do not alter the fundamental pathology in the heart but do relieve satisfactorily the distressing symptoms caused by pulmonary stenosis. Until researches on intra-cardiac surgery point the way to a means of permanently relieving pulmonary stenosis, some means of increasing the flow of blood to the lungs by circumventing the obstruction must be employed.

CHOICE OF PATIENTS FOR OPERATION

The assumption that all cyanotic children with congenital heart disease may be benefited by surgery is sadly erroneous. The incapacitated child with a typical tetralogy of Fallot who has an elevated red blood cell count, a normal or boot-shaped heart, a systolic murmur at the base of the heart, clear lung fields, and deviation of the axis to the right in the electrocardiogram can almost always be relieved by surgery. Unfortunately, only about 60 per cent of cyanotic children with congenital heart disease fall in this typical group. The other 40 per cent have all sorts of cardiac and large vessel anomalies, many of which are not remediable by any surgical procedure known to date. Selection of patients suitable for operation from this latter group requires a profound clinical knowledge of congenital heart disease. The diagnostic work in this series of 181 patients forming the basis of this surgical report, was done by Dr. Stanley Gibson and his associates, Drs. Frank Dammann, Jakub Schlichter and Edwin Leach.

It is our policy to refuse operation to no child regardless of its condition if it can be demonstrated that cyanosis is due to diminished blood flow to the lungs. It has become apparent that the best clinical results follow surgery on patients with classical tetralogy of Fallot. Patients who have pure pulmonary stenosis or pulmonary stenosis associated with other cardiac defects such as tricuspid atresia or a single ventricle, may anticipate less satisfactory postoper-

* Read before the American Surgical Association, St. Louis, Mo., April 20, 1949.

ative improvement. Parents are apprised of this fact before operation. It is our policy routinely to advise parents that every operation must be considered an exploratory procedure because occasionally a seemingly typical case may have abnormalities which preclude surgical relief.

The ages of these 181 patients varied from 10 weeks to 17 years. Children below one year of age are operated upon, not by choice, but only because they cannot live unless more blood is shunted to the lungs. Most of the infants below one year of age in this series were so severely hypoxic that intermittent or continuous oxygen administration was necessary.

PREOPERATIVE CARE

Regardless of the fact that diagnostic procedures have been completed in the outpatient department, cyanotic children are admitted to the hospital a minimum of 48 hours before the morning of operation. During this time observation is close for any signs of upper-respiratory infection. It is difficult in the deeply cyanotic child to evaluate a red throat or an inflamed ear drum. Rectal temperatures of 100 degrees to 100.5 degrees F are not uncommon in the apprehensive child and if unaccompanied by any sign of cough, snuffles or contagious disease, are disregarded. Many children have had to be sent home because of the upper-respiratory infections to which they are extremely susceptible. It is, of course, contraindicated to operate on a cyanotic child with an upper-respiratory infection. At the same time it is hazardous to delay operation in the very cyanotic child because of the frequency of cerebral accidents during such infections. An infant, age six months, with a slight cold, extremely cyanotic and in desperate condition was brought in from a far western state. The danger of sending the child home seemed greater than that of intratracheal anesthesia and surgery. It died of overwhelming pneumonia five days after successful aortic-pulmonary anastomosis.

Penicillin in 100,000 unit doses twice daily is begun at least 24 hours before operation.

The apprehensive child—this includes most of them—is beneficially quieted by appropriate medication with the barbituric acid derivatives. Psychic sedation of the child, and incidentally of the parents, is routine.

Preoperative medication given one hour before operation is ordered by the anesthesiologist, Dr. William O. McQuiston. He³ advises relatively large doses of morphine and atropine for children below five years of age, including infants, and morphine and scopolamine for all patients above five years of age. For example, a three month old infant weighing eight pounds is given hypodermically morphine sulphate gr 1/48 (1.3 mg) and atropine sulphate gr 1/300 (0.2 mg). A four year old child receives morphine sulphate gr 1/8 (8 mg) and atropine sulphate gr 1/200 (0.3 mg). From five years of age until puberty, preoperative medication consists of morphine sulphate gr 1/8 (8 mg) and scopolamine hydrobromide gr 1/200 (0.3 mg). Age, not weight, determines the size of the dose. The patient should be drowsy and indifferent to surroundings when arriving in the operating room.

ANESTHESIA

In no group of patients is the skill and resourcefulness of a trained anesthesiologist more essential. The already hypoxic patient must be carried through a still more severe period of oxygen deprivation occasioned by opening the chest and occluding for a time one pulmonary artery. Doctor McQuiston has found cyclopropane the most satisfactory anesthetic agent because it allows a high concentration of oxygen and minute to minute control of the depth of anesthesia. Intubation is essential to secure an adequate airway and make possible reexpansion of the lung on a moment's notice. The operative technic is greatly facilitated if the anesthesiologist controls all respiratory movements, *i e*, "breathes for the patient" by rapid intermittent pressure on the anesthetic bag. Respiratory efforts during controlled respiration indicate increasing hypoxia and carbon dioxide excess and are best relieved by temporarily discontinuing the operation and reexpanding the lung if the pulmonary artery has not yet been occluded in preparation for the anastomosis. Curare is used only when it is impossible otherwise to quiet the operative field during the actual anastomosis.

Cardiac arrhythmias have not resulted from the use of cyclopropane anesthesia.

Bradycardia during operation has been benefited by intravenous administration of a very small dose of atropine, often as little as 1/1000 of a grain. Acute bradycardia or arrhythmia initiated by vagal reflexes occurring usually as dissection of the pulmonary artery is begun have been treated most satisfactorily by swabbing the hilus of the lung and the vagus nerve with a solution of 5 per cent cocaine.

TEMPERATURE CONTROL DURING OPERATION

Elevation of temperature during any prolonged operation is expected but if controlled usually occasions no anxiety. During operations on cyanotic children we have noted a more than average rise in temperature. With each degree of elevation in temperature there is approximately a 7 per cent increase in metabolism and a consequent increase in oxygen consumption. Since hypoxia is one of the chief causes of death during operation for pulmonary stenosis it follows that any means of lessening the consumption of already inadequately available oxygen is in order. For years the importance of maintaining body temperature during operation has been taught but misinterpreted. Elevation of temperature above normal during any operation is unjustifiable. McQuiston³ suggested in May of 1948 that since no means of supplying oxygen extrapulmonically has been successful we attack the problem from the other side and try conserving oxygen by lowering the body temperature during operation in patients with severe cyanosis. About this time an infant Thomas O. three months and 25 days old with marked cyanosis since the age of two months was flown to the Children's Memorial Hospital as an emergency. Attacks of unconsciousness lasting about 30 minutes were precipitated by the slightest

exertion Even in oxygen his condition was precarious It was the opinion of the cardiologists, anesthesiologist and surgeon that the infant would probably die on the operating table

The usual preparations for operation were observed The infant received hypodermically morphine sulphate gr 1/60 (1 mg) and atropine sulphate gr 1/300 (0.2 mg) one hour before operation (Dr John A Bigler, with the help of the Central Scientific Company,* Chicago, Illinois, had previously constructed an explosion-proof apparatus for the continuous recording of rectal temperatures Later Doctor Bigler had a water mattress constructed for the control of temperatures) Cyclopropane anesthesia was used The infant was surrounded with ice bags His temperature was lowered until it registered 96 degrees F rectally, and was kept at this level for approximately 90 minutes During much of this time no cyclopropane was necessary to maintain anesthesia When the aortic-pulmonary anastomosis had been completed, hot water bottles were substituted and the temperature was slowly returned to normal As soon as the temperature reached 96.7 degrees F during closure of the chest, the infant began to react and required a small amount of cyclopropane He was returned to his room awake and in good condition After 24 hours he was removed from oxygen and was taking a full formula by bottle He was discharged 14 days after operation in excellent condition

Since then Doctor McQuiston has used controlled hypothermia during operation of 71 patients with pulmonary stenosis No deleterious effects have been noticed There has been no increase in postoperative respiratory complications We believe—considering previous patients as controls—that the mortality and morbidity from severe anoxia has been lessened by the use of hypothermia

SURGICAL TECHNIC

Aortic-pulmonary anastomosis Although the technic of aortic-pulmonary anastomosis has been outlined in previous publications it is reviewed in detail in an attempt to answer the most commonly asked questions

The child is laid supine on the operating table on a water mattress covered with a sheet, and anesthetized The mattress connected with an inflow and outflow tube is partially filled with tap water As the operation progresses, cool or even ice water is funneled into the water mattress to keep the patient's rectal temperature at about 99 degrees F Only the very cyanotic children are cooled to 96 or 97 degrees F It is desirable to have a continuous recording of the temperature when refrigeration is being used After the child has been anesthetized a cannula is inserted in the right saphenous vein at the ankle for the administration of fluids, blood and medication as needed during and following operation The child is then turned on its right side and fixed in this position with a long strip of adhesive tape across the hips and attached to the operating table to keep the child from rolling on the water mattress The

* Construction of apparatus by M. N. States, Ph D, and H. M. Sullivan, Ph D

thermocouple is inserted in the rectum and fixed with adhesive tape to prevent its being ejected. Skin preparation is with ether, iodine and alcohol.

The incision is begun anteriorly about 1 inch below and slightly lateral to the left nipple, continued straight back beneath the tip of the scapula and curved upward behind the middle of the scapula (Fig 1A). The muscles are cut about 1 cm. below the tip of the scapula and the fourth rib is identified by palpating from the first rib downward. The chest is routinely opened through the fourth interspace except in older children or those with large chests in

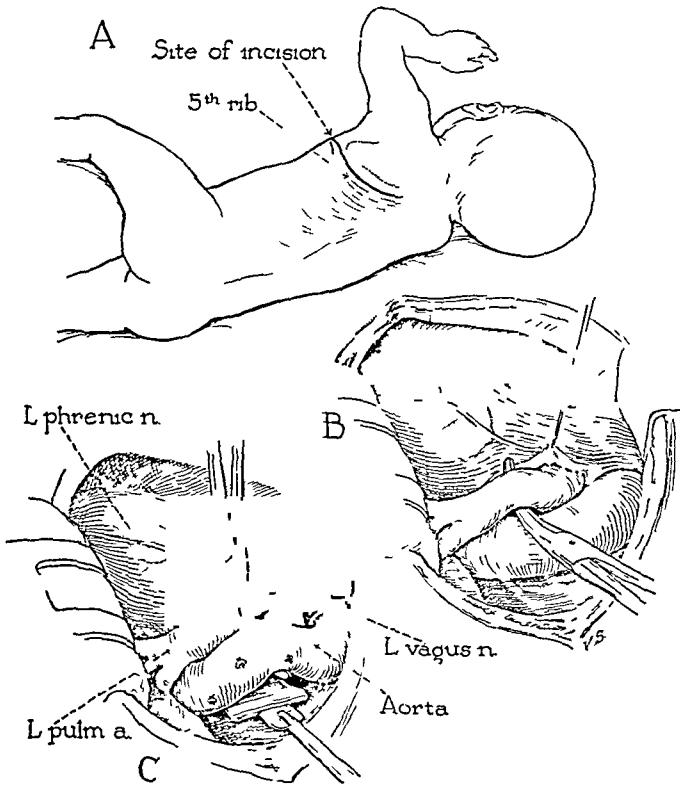


FIG 1—Technic of aortic-pulmonary anastomosis
A Lateral incision through the left fourth interspace
B The pulmonary artery is thoroughly freed from surrounding structures
C The aorta is elevated with a cystic duct forceps as the aortic clamp is slipped beneath it

which cases the fourth rib is resected subperiosteally. The parietal pleura over the hilus of the lung is opened and the pulmonary artery identified. Exposure of this vessel will be tremendously simplified and expedited if the adventitial layer about the vessel is identified and the dissection carried through this layer.

In general the deeply cyanotic child has a smaller than average pulmonary artery buried in masses of dense connective tissue and thin-walled veins. Sponges are not used during the dissection because they are traumatic and relatively ineffective. A stream of saline solution delivered from a bulb syringe and removed by an aspirator is far more effective than sponges for

clearing away spilled blood The pulmonary artery, including its primary branches—usually three—is well freed from surrounding structures (Fig 1B)

The lateral edge of the parietal pleura which was cut to free the pulmonary artery is dissected laterally to expose the aorta from its medial surface Sometimes the vagus nerve lies anteriorly and must be freed from this layer of pleura but more often it lies deep and is not seen until later This fold of pleura is caught with a stitch drawn laterally and held with a hemostat As in dissection of the pulmonary artery it is well to follow the adventitial layer in freeing the aorta However, the walls of the aorta should not be closely skinned because in so doing some of the blood supply derived from small adventitial vessels is destroyed

Intercostal arteries vary tremendously in number and position At the proper level opposite the pulmonary artery enough of them are doubly tied and cut to make room for application of the clamp The average number of intercostals requiring ligation is four Occasionally a vessel 2 to 3 mm in diameter arising from the aorta at this level cannot be identified as an intercostal or a bronchial artery If the vessel is directed downward, presumably towards the lung, every effort is made to avoid sacrificing it although no deleterious effects have been noted when such vessels have been ligated and cut

At this point the lung is usually reexpanded for a few minutes even though the patient's condition seems good The added oxygen absorbed is good insurance against the period of increased hypoxia necessitated by occluding the pulmonary artery during the anastomosis The lung is deflated and doubly encircling ligatures of heavy silk, oiled to prevent sticking in the adventitia, are placed around the pulmonary artery and around each of its branches These ligatures may be put on later after the aortic clamp has been applied (Fig 2E)

The aorta, well freed, is then elevated with a cystic duct forceps and the lower half of the proper sized aortic clamp is slipped beneath the vessel (Fig 1C) (If the clamp does not go into position easily, the reason usually is that a posterior lying intercostal artery has been overlooked) The upper half of the clamp is adjusted As the sections of the clamp are being brought together the adventitia of the segment of aorta which is to be isolated is grasped with a tissue forceps and drawn away from the clamp to increase the size of the occluded segment It is essential to determine by inspection or by palpation of a thrill distal to the clamp that some blood is going through the aorta after the clamp has been tightened How tight should the clamp be screwed? That will have to be learned from animal experimentation It needs only to be snug It is reassuring once or twice during the anastomosis to try the knuiled nut on the end of the clamp to be sure it is not loosening spontaneously or that the assistant holding the clamp has not inadvertently loosened it I have never had the isolated segment of aorta slip out of the clamp but it could happen with rather terrifying results

The excess adventitia is removed with scissors from the occluded portion of the aorta where the anastomosis is to be made

FIG 2 (Legend on opposite page)

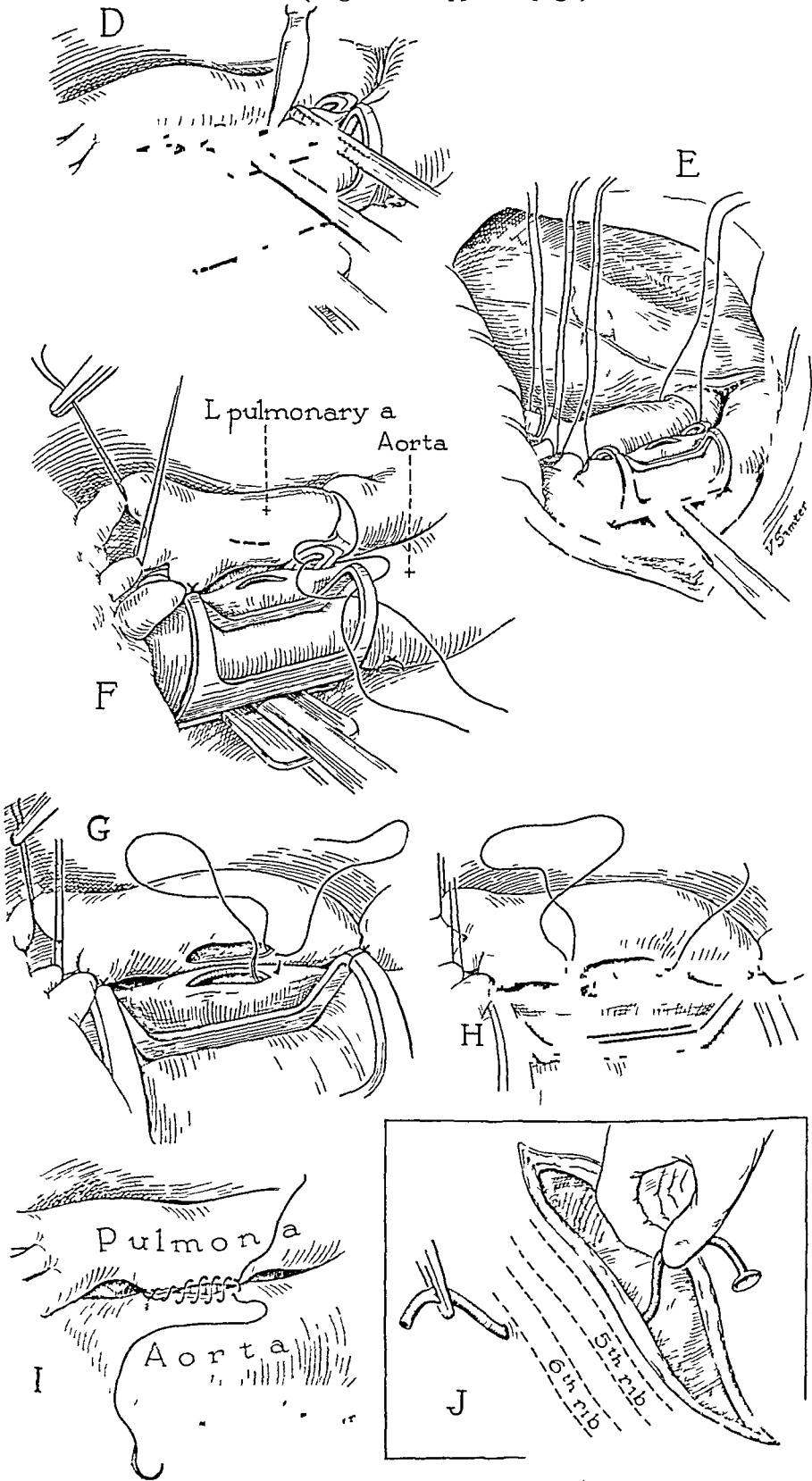


FIG 3 (Legend on opposite page)

The incision in the aorta must be carefully and accurately made in exactly the right place (Fig 2D) With the open ends of a fine tissue forceps the rounded portion of the occluded segment of aorta is flattened by gentle pressure The knife—a small blunt blade with a long handle—is directed at right angles to the flattened wall of the aorta and exactly toward the middle of the occluded portion, so that the anterior and posterior lips will be equally wide (Fig 2D) If the incision is made off from the midline, either the anterior or posterior lip will be short and one of the rows of sutures will be put in with great difficulty The knife is used only to make a tiny opening in the aorta The incision is then completed to $\frac{1}{4}$ inch (6.3 mm) with a fine pointed, angled scissors There will be no fragmentation of the aorta in children if it is carefully cut with a scissors (Many surgeons practicing this operation on dogs have reported difficulty occasioned by the tendency of a dog's aorta to fragment while being incised and sutured It must not be forgotten that most laboratory dogs are full grown and many are old Their aortas compare in age with those of a 30 to a 60 year old person If gently handled, fragmentation of the edges of the cut aorta in a child need not be feared)

The pulmonary artery is now tied to the aortic clamp One end of the doubly encircling ligature about the large branch or branches of the pulmonary artery nearest the aorta is threaded through the flanges of the lower side of the aortic clamp The other end of this ligature is drawn through in the opposite direction (Fig 2F) These ligatures are most easily threaded on the clamp by using a large needle from which the point has been broken off for safety's sake The pulmonary artery is then held against the aortic clamp with a cystic duct forceps while the ligature is being drawn up snugly and tied The ligature about the pulmonary artery is tied to the upper side of the aortic clamp in a similar fashion By tying the proximal ligature second the occluded portion of the pulmonary artery is distended with blood, making it far easier to choose the correct site for incision The hemostat is left on the remaining medial branch of the pulmonary artery and a bit of traction kept on it after making the incision in the pulmonary artery to keep the hole open and its edges visible The incision in the pulmonary artery is made with a knife and enlarged to proper size with a scissors to match the incision in the aorta

FIG 2—Technic of aortic-pulmonary anastomosis continued

D Incision in the aorta must be in exactly the right place (see text)

E Ligatures of heavy oiled silk are placed around the left pulmonary artery and its branches

F The lower branch of the pulmonary artery is tied to the lower edges of the clamp first, then the main vessel is tied to the upper part of the clamp

FIG 3—Technic of aortic-pulmonary anastomosis continued

G The first stitch is so placed that the knot is outside the lumen of the vessel

H The posterior row of stitches, as well as the two at the lower angle, coapt the edges of the vessels adventitia to adventitia

I The anterior row of sutures is left loose until all the stitches have been placed The entire anastomosis is done with one continuous suture

J The chest is routinely drained with a de Pezzer catheter through the sixth interspace

The isolated segment of aorta and the occluded portion of the pulmonary artery are now washed free of all blood by a stream of saline solution. In a few instances blood has seeped into the occluded portion of the pulmonary artery. This has been due to failure to tie tightly enough one or both of the ligatures holding the pulmonary artery to the aortic clamp. The error is easily corrected by grasping the knot with a hemostat, drawing up the slack and tying a thread around the pulmonary ligature just below the knot.

The anastomosis, performed with 00000 Deknatel silk on a curved No 9 atraumatic needle, is begun at the superior angle. The suture is carried through the pulmonary artery from the outside in and through the aorta from the inside out and tied. The knot is, therefore, outside of the lumen of the vessel (Fig 3G). Continuing with the suture in an over-and-over manner the posterior cut edge of the pulmonary is sewed to the posterior cut edge of the aorta, adventitia to adventitia. The stitches are placed 1 mm apart and about 1 mm from the cut edges. It is absolutely essential that every stitch goes through all layers of the aorta. At the inferior angle the method of suture is not changed but it is necessary to carry the needle through each vessel wall separately (Fig 3H). We do not lock the suture at the inferior angle as previously suggested but continue with this thread to bring the anterior cut edges of the vessels together intima to intima. While putting in the posterior row of stitches and those in the lower angle, the thread is drawn up gently to coapt the edges as each stitch is placed. However while placing the anterior row of sutures the thread is left loose until the last stitch has been placed. This method allows visualization and accurate placement of each stitch. Beginning then at the lower angle of the anastomosis the thread is grasped with fine tooth forceps and each stitch is drawn up with proper tension. The ends are tied and the anastomosis is complete (Fig 3I).

The hemostat on the branch of the pulmonary artery is released first, then the lower pulmonary ligature is cut and finally the upper pulmonary ligature is cut. A small amount of bleeding may occur through the needle holes but it stops spontaneously. If the sewing has been inaccurate at any point an extra interrupted stitch may be necessary. We have never had bleeding from the posterior row of stitches. Should it occur, one would have no choice but to take down the entire anastomosis and do it over.

The aortic clamp is released *slowly*. Partial occlusion of the aorta has elevated the brachial blood pressure usually from 10 to 20 mm of mercury, and to avoid a precipitous fall it is wise to release the clamp a bit at a time while the blood pressure is being checked. If the blood pressure drops more than approximately 20 mm of mercury the clamp is tightened somewhat for a few minutes and again slowly released. The aortic clamp is removed. Palpation over the anastomotic channel will reveal a thrill caused by blood flowing from the aorta into the pulmonary artery. The lung is fully reexpanded by the anesthesiologist. Every chest is drained. A de Pezzer catheter with all but a flange cut away is drawn from the inside out through a tiny stab wound in the sixth

interspace (Fig 3J) The flange of the catheter is placed snugly against the inside of the chest

Adjoining ribs are drawn together with two heavy catgut sutures placed subperiosteally on the inferior rib to avoid pressure on the intercostal nerve The muscles and subcutaneous tissue are closed in layers with continuous sutures of 000 chromic catgut The slight and questionable disadvantage of closing the chest with catgut instead of silk, I believe, is more than offset by the operating time saved in putting in continuous sutures The operating time from skin incision to skin closure varies from one and a half to two hours

While the anesthesiologist is making pressure on the anesthetic bag to force all air from the chest a hemostat is clamped on the drainage catheter

The patient is turned very slowly from the lateral to the supine position For some unknown reason the blood pressure is apt to drop alarmingly at times as the position is being changed The intratracheal catheter is not removed until the child begins to react Some poor risk patients who have been very hypoxic during the operation breathe very poorly for a time immediately after surgery Such patients are kept on the operating table until they are breathing normally and their systolic blood pressure has returned to approximately 100 mm of mercury Occasionally a child has been kept on the table from two to three hours after the operation before it has been considered safe to move it During this time full oxygen is given by intermittent pressure on the anesthetic bag Respiration stimulating drugs are never used No drug is superior to oxygen for the child who is near death from hypoxia

SUBCLAVIAN-PULMONARY ANASTOMOSIS

Anastomosis of the proximal end of the left subclavian artery to the side of the left pulmonary artery has been accomplished successfully in 14 patients with right aortic arches Surgical approach is the same as for aortic-pulmonary anastomosis—through the left fourth interspace or through the bed of resected fourth rib After freeing the pulmonary artery as described above, the subclavian artery is freed from its surrounding structures to its origin from the innominate artery The vagus nerve and its recurrent laryngeal branch looped around the subclavian artery are identified and thoroughly freed Instead of ligating the subclavian artery at its point of branching, the individual branches, usually three, are ligated separately each with one well placed ligature A ductus clamp, previously described,⁴ the basic principle of which is multiple tiny teeth in the apposing jaws to prevent slipping, is now placed on the subclavian artery a proper distance proximal to the point where the subclavian artery is to be cut (Fig 4A) The subclavian artery is cut squarely across just proximal to its point of branching and is drawn out of the recurrent nerve loop and turned downward To gain added length the subclavian artery is well freed from the carotid artery at their common point of origin The proximal end of the pulmonary artery is now occluded with another ductus clamp or one of its modifications (Fig 4B) The branches of the pulmonary artery are

FIG 4 (Legend on opposite page)

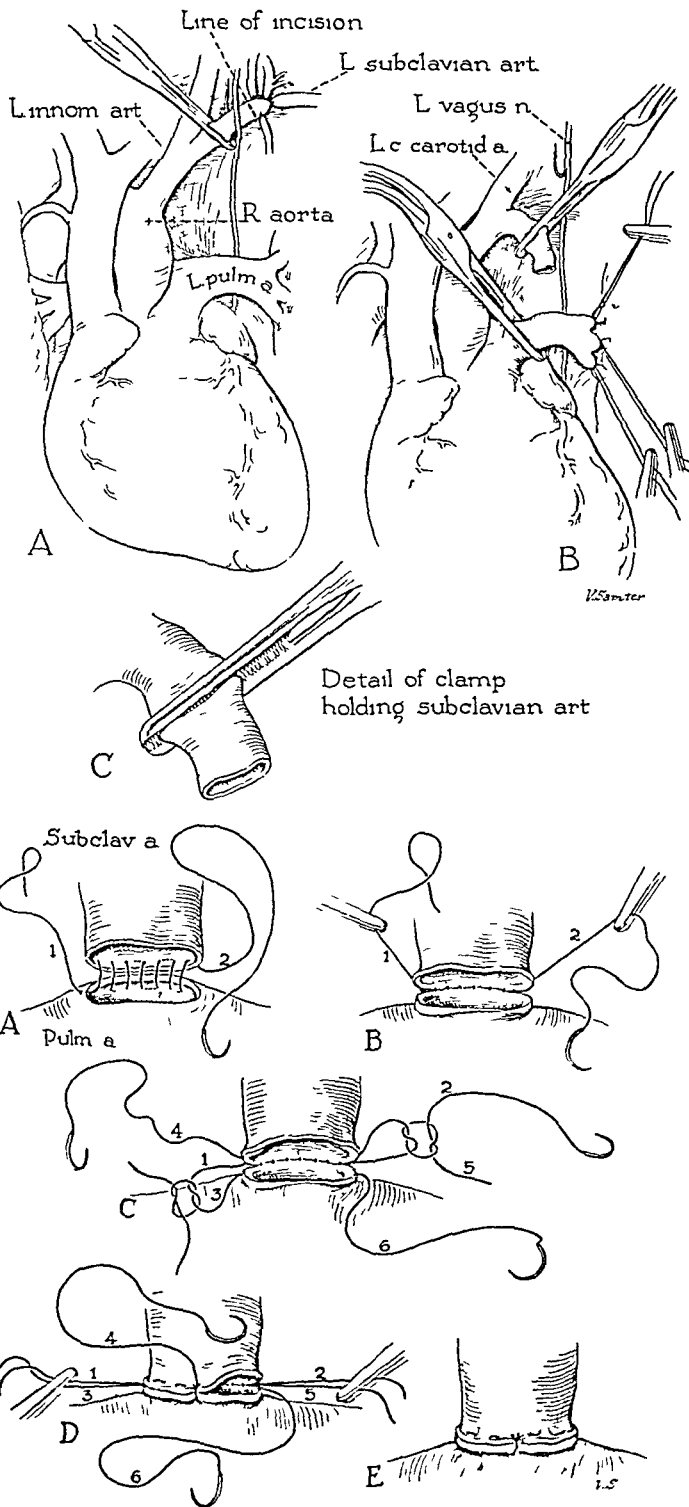


FIG 5 (Legend on opposite page)

occluded with doubly encircling ligatures held taut with hemostats. The technic of anastomosis is that described by Blalock (Fig 5A-E)

Our surgical approach to the patient with pulmonary stenosis and a right aortic arch has changed (Table I). We rather stubbornly performed 22 consecutive aortic-pulmonary anastomoses on the right side in patients ranging in age from four months to 16 years. In no case was it impossible to perform the anastomosis if a proper sized pulmonary was present. However, this operation is difficult on the right side because the right pulmonary artery is short and courses at a 90 degree angle to the aorta. Furthermore, the bronchus lies in the way between the pulmonary artery and the aorta. While the results eventually were satisfactory a number of children did not have an immediate typical continuous murmur and were not promptly relieved of their cyanosis following operation. Improvement was slow over a period of two to three weeks but eventually was satisfactory. One child had partial atelectasis of the lung and a bad cough, presumably due to pressure of the anastomosed vessels on the bronchus. The anastomotic channel in one child closed about four months after aortic-pulmonary anastomosis on the right side. A subclavian-pulmonary anastomosis was later done on the left side with a good result.

Our policy now is as follows. The surgical approach in all children above two years of age with pulmonary stenosis is through the *left fourth interspace*. If the arch of the aorta curves to the left an aortic-pulmonary anastomosis is done. If the arch curves to the right a subclavian-pulmonary anastomosis is done. In infants below one year of age with a right arch the subclavian artery on the left is apt to be too small for a satisfactory anastomosis and the approach is on the right side for an aortic-pulmonary anastomosis. Children between one and two years of age vary in size and the judgment (or guess work) of the operator will have to determine which side to approach. In a 15-month-old child with a right aortic arch we found a good-sized left subclavian artery and anastomosed it satisfactorily to the left pulmonary artery.

It appears that in children with left aortic arches an aortic-pulmonary anastomosis is technically simpler than a subclavian-pulmonary anastomosis on the right side, that in children with right aortic arches subclavian-pulmonary anastomosis on the left side is technically simpler than aortic-pulmonary anastomosis on the right side.

POSTOPERATIVE CARE

The anesthesiologist and the resident accompany the patient back to the room. The patient is placed in an oxygen tent rather routinely for 24 hours,

FIG 4—Technic of subclavian-pulmonary anastomosis

A The branches of the subclavian artery are tied individually, the vessel occluded with a ductus clamp and cut at the dotted line.

B A ductus clamp or one of its modifications is applied to the left pulmonary artery. The branches are occluded with doubly encircling ligatures of heavy silk.

C Enlarged drawing to illustrate the ductus clamp with many fine teeth in the apposing jaws which occlude, will not slip and will not injure the vessel wall.

FIG 5—A to E. Technic of subclavian-pulmonary anastomosis according to Blalock.

longer if necessary. A glass tube is used to connect the chest drain catheter with a tube in an under-water seal bottle. This allows easy inspection of the type of drainage from the chest. The water seal bottle is fixed to the floor with adhesive tape to prevent its being kicked over and to prevent the curious from raising the bottle. The water level in the bottle is marked by a strip of adhesive tape so that the nurse may recognize at a glance the amount of drainage from the chest. (See complications.)

TABLE I—*Surgical Treatment of Patients with Right Aortic Arches**

Operation	Number	Deaths	Mortality
Aortic pul anas	22	2	9%
Subcl pul anas	14	0	0
Explor only (No pul art)	5	2	40%
Totals	41	4	9.7%

* 22 per cent of the patients with pulmonary stenosis had right aortic arches

A 50 cc syringe and aspirating needle are kept at the patient's bedside. A catheter attached to an aspirating machine is used to aspirate mucus from the throat. If the rattling mucus cannot be reached the stimulus of the catheter in the throat is often effective in stimulating a productive cough. Careful

TABLE II—*Postoperative Complications in Patients Who Recovered*

Pulmonary Complications	No. of Cases
Cough	22
Laryngeal edema	7
Laryngeal edema requiring tracheotomy	3
Atelectasis	4
Pulmonary edema	3
Pneumothorax	3* 5
Mild hemothorax	2* 4
Hemopneumothorax	1* 1
Effusion	3* 6
Hemorrhage	3
Pneumonia	1
Other Complications	
Cerebral anoxia	
With coma 4 days 1	2
With coma 3 days 1	
With temporary spasticity	3
Tonsillitis	2
Anuria (transfusion reaction)	1
Wound infection severe	1* 1
Pulmonary embolus	1
Horner's syndrome following subclavian pul anas on rt side	2

* Untrained cases

observation for obstructed respiration manifested by labored breathing and suprasternal retraction is important and calls for immediate removal to the steam room.

Penicillin units 100,000 is given intramuscularly twice a day for approximately a week following operation.

The drain is removed from the chest on the second or third day.

POSTOPERATIVE COMPLICATIONS

As might be anticipated, by far the largest group of postoperative complications were pulmonary (Table II) Laryngeal edema occurring in ten patients was due most likely to irritation of the intratracheal anesthetic tube Patients are watched very carefully following operation for any sign of laryngeal obstruction and promptly moved to the steam room if respiration is labored If respiration is obstructed so that the patient fights for air, or if obstructed respiration persists and the patient becomes fatigued, a tracheotomy is promptly done There is less danger in doing an occasionally unnecessary tracheotomy than in waiting too long to relieve the patient's struggle for air

Should the chest be drained? is a question often asked From our experience the answer is an unequivocal "yes" The first 13 patients operated upon for pulmonary stenosis were not drained and nine required one or more aspirations of the chest for the removal of fluid and/or air Furthermore, these patients required repeated roentgen ray examination of the chest The following 160 patients were drained and only seven required aspiration, because for one reason or another the drainage tube did not function efficiently Observation of the rise and fall of the fluid in the under-water tube with each respiration reveals at a glance whether the drainage tube is functioning properly Marking the fluid level in the drainage bottle immediately after operation makes it simple to estimate the amount of postoperative drainage Auscultation of the chest determines whether the lung is being aerated Postoperative roentgenological examination is practically never necessary except for study of conditions other than the accumulation of fluid or air

Non-fatal, severe postoperative hemorrhage in the left pleural cavity occurred three times At re-operation in one case the bleeding was found to come from the cut end of a rib which had been removed subperiosteally The cause of bleeding in the other two was not determined It stopped spontaneously In all of these cases the hemorrhage was promptly detected by observation of the drainage tube and bottle Blood was replaced by transfusion as it was being lost Without a safety valve drainage tube the hemorrhage might not have been detected early, and the amount of blood to be replaced would have been less accurately known

Anoxia during operation is difficult to combat and will be followed by cerebral symptoms or death depending upon the degree of deprivation Five patients showed the effects of non-fatal cerebral anoxia following operation—two had prolonged coma and three had temporary spasticity The only treatment employed besides the usual intravenous alimentation and careful nursing was the administration of a high concentration of oxygen We have been singularly fortunate in that the patients who suffered from cerebral anoxia all recovered completely or died Nothing is more tragic than the survival of a child who, following operation, is merely an unthinking metabolic machine

Lesser complications require no discussion, minor complications which did not influence recovery unfavorably are not listed

DISCUSSION OF DEATHS

For the causes of death in 16 patients following a successful aortic-pulmonary anastomosis see Table III. Postmortem examination was obtained on all but one. It will be noted that six deaths were due to cerebral accident. This catastrophe is very common before as well as after surgery, in fact, more children died of this complication between the time they were examined and were

TABLE III—*Causes of Death Following Anastomosis*

Age	Number of Cases	Deaths	Time Following Operation	Causes of Death
10 wks - 1 yr	17	5	8 days 16 days 5 days 7 days	Pneumonia Right heart failure Cerebral anoxia Heart failure anoxia thrombosis of anastomosis
1-2 yrs	22	4	5 hours 16 hours 15 hours 4 days 8 weeks	Thrombosis cerebral sinuses Hemorrhage ruptured bronchial artery Cerebral thrombosis Cerebral hemorrhage Sepsis infected vegetations at anasto- mosis secondary to saphenous vein infection at site of cannula insertion
2-3 yrs	20	3	36 hours 7 days 20 days	Cerebral hemorrhage Thrombosis anastomotic site saddle embolus Died following embolectomy Sepsis multiple abscesses of the left lung Anastomosis patent
3-4 yrs	18	0		
4-5 yrs	18	1	5 hours	Tension pneumothorax
5-6 yrs	14	1	During operation	Anoxia
6-7 yrs	12	0		
7-8 yrs	13	0		
8-9 yrs	8	0		
9-10 yrs	6	0		
10-11 yrs	2	1	18 hours	Hemorrhage from intercostal artery
11-12 yrs	9	1	30 hours	Cerebral hemorrhage
12-16 yrs	6	0		
Totals	165	16	Mortality of 9.7%	

awaiting surgery than died of it following surgery. Basically, hypoxia is the cause of these deaths, and so long as it cannot be relieved during operation unavoidable deaths will occur.

Two children died of heart failure. Both had had decompensation relieved by digitalis before surgery. The child who has cardiac enlargement, whose liver is down, and who has previously suffered cardiac embarrassment is a very poor operative risk.

One child died the night after operation of hemorrhage from a small open intercostal artery. Either the ligature slipped off or the vessel was not tied. This child need not have died. At that time we were using plain sterile water in the drainage bottle. What blood drained into the bottle was promptly hemolyzed and did not look red enough to the nurse to sound an alarm. When the

pulse became weak the significance of the "pink drainage" was recognized but it was too late. We now use saline in the drainage bottle, observe and mark the fluid level frequently.

One child died of tension pneumothorax before it was routine to drain the chest. At operation adhesions were separated at the apex of the lung. Upon completion of the operation the lungs were inflated and the left chest filled with saline solution. No bubbles were seen. However, a few hours after operation the child suddenly became dyspneic and died. Postmortem examination revealed the cause—tension pneumothorax from the escape of air from the apex of the lung. Since then we have drained all chests.

The case of death from a ruptured bronchial artery or a ruptured ductus arteriosus requires some explanation. At operation this child had no pulmonary artery on the left side. However, arising from the arch of the aorta just beyond the origin of the left common carotid artery was a vessel which coursed to the hilus of the left lung. The proximal 1.5 cm. of this vessel was hard and obviously occluded. Slightly above the hilus of the lung it expanded into a non-pulsating, extremely thin-walled vessel about 5 mm. in diameter. An anastomosis between this vessel, a bronchial artery or a partially obliterated ductus arteriosus, and the aorta was made. Upon release of the clamp there was a brisk thrill over the anastomotic channel. Sixteen hours after operation there was a sudden gush of blood from the drainage tube and the child died. At postmortem examination it was found that the bronchial artery or ductus arteriosus had ruptured distal to the site of anastomosis to the aorta. The anastomosis was intact, measured 4 mm. in diameter and was patent. It can only be assumed that this vessel could not withstand the strain of aortic blood pressure. It is interesting that the vessel rather than the anastomosis gave way. Further postmortem examination revealed a single pulmonary artery going to the right lung—not even a remnant of a left pulmonary artery was found. (Since this time we have performed a similar operation on an 18-month-old child with a fair result.)

The cause of death following exploration only was anoxia in six cases and anoxia and bilateral bronchopneumonia in one case. Postmortem examination was obtained in all cases. In six of these cases the pulmonary artery was merely a tiny strand of bloodless tissue and in one the pulmonary artery was present but too small for an anastomosis. In nine exploratory operations followed by survival no pulmonary artery could be found but, of course, proof of its absence is lacking.

If blood cannot be shunted to the lungs even simple exploration is apt to terminate fatally.

MORTALITY STATISTICS

Mortality statistics are always fascinating because they prove so little and can be made to prove so much (see Table IV). There were 16 deaths in 165 patients upon whom an aortic-pulmonary or subclavian-pulmonary anastomosis

was done, a mortality of 9.7 per cent. Exploratory operation alone was done on 16 patients with seven deaths or a mortality of 43.8 per cent. The overall mortality—23 deaths in 181 operations—is 12.7 per cent. There were 12 deaths in 59 children below three years of age upon whom an anastomosis was done, or a mortality of 20 per cent, while in 106 children from three to

TABLE IV—*Mortality Statistics*

Following Anastomosis Ages	Cases	Deaths	Percentage
10 weeks–3 years	59	12	20
3–16 years	106	4	3.8
Total	165	16	9.7
Exploratory Operations	16	7	43.8
Grand total	181	23	12.7



A

B

FIG 6—A Preoperative roentgenogram of first patient, D. S., to have an aortic-pulmonary anastomosis, September 13, 1946.

B Roentgenogram two years later showing about the usual postoperative enlargement of the heart and the increase in vascularity of the lung fields.

16 years of age there were only four deaths or a mortality of 3.8 per cent. In the first 10 cases below one year of age reported by Potts and Gibson⁷ there was only one death, or a mortality of 10 per cent. Four of the next seven patients died and now the mortality in children below one year of age operated upon for congenital pulmonary stenosis is 30 per cent. Statistics are interesting.

RESULTS

The results in 135 patients who survived aortic-pulmonary anastomosis and in 14 patients who survived subclavian-pulmonary anastomosis have been satisfactory to us, spectacular to the parents, and acceptable to the children. The medical and surgical staff realize that the fundamental pathology in the heart has not been corrected and, what is more, that an added burden has been placed upon the heart by the surgical procedure. The parents see only the change in the child's color and are grateful for release from the anguish of being powerless to relieve their unhappy child. The child nonchalantly accepts his improved condition, runs and plays without thought of protecting his heart muscle.

What is the ultimate prognosis? This question is asked again and again. Too few years have passed to even guess intelligently the future of these children. Every child has some enlargement of the heart rather promptly following operation. In most instances the enlargement soon stabilizes itself—is not progressive. In Fig 6A is shown a roentgenogram of D. S., the first patient to have an aortic-pulmonary anastomosis, operated upon September 13, 1946. Fig 6B is a roentgenogram taken two years later. Enlargement of the heart is moderate. A few of our patients have shown excessive cardiac enlargement and two have gone into heart failure. For these I am to blame. The anastomotic channel was made too large. In the early cases we made incisions in the aorta and pulmonary artery from 5/16 to 6/16 of an inch long. *This opening was too large.* Now on young and older children alike, we routinely make the incisions in the vessels 4/16 of an inch (6.3 mm) long, accurately measured with a caliper. This opening is large enough to relieve the major portion of the cyanosis. It is difficult in dogs to make the opening much smaller than 4/16 of an inch and have it remain patent. This undoubtedly is true for children. We still have not answered the question of whether the hole will grow with the child.

To the best of our knowledge only one anastomotic channel has closed in 149 patients who were operated upon during the past two and one-half years and survived surgery.

SUMMARY

- 1 One hundred and eighty-one patients with congenital pulmonary stenosis have been operated upon at the Children's Memorial Hospital.
- 2 No patient regardless of condition, has been refused surgery if it could be demonstrated that there was diminished blood flow to the lungs.
- 3 The importance of skilled anesthesia is stressed. Cooling the patients during operation is beneficial because it lessens the consumption of oxygen.
- 4 The technic of aortic-pulmonary anastomosis on the left side is outlined in detail.
- 5 Subclavian-pulmonary anastomosis on the left is done on children above two years of age with right aortic arches.

6 Postoperative complications and deaths are outlined and discussed

7 The overall mortality rate, 23 deaths in 181 patients, is 12.7 per cent. The mortality rate in patients upon whom anastomoses could be performed, 16 deaths in 165 patients, is 9.7 per cent

8 The results in those patients who survived surgery have been very satisfactory

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DISCUSSION—DR H. WILLIAM SCOTT, JR., Baltimore. The point that Dr. Potts made about cooling the patient certainly seems to be a good one. It is our experience at Hopkins that the majority of deaths encountered during the course of operation on cyanotic patients seem to be due to cardiac anoxia. Cooling the patient by lowering the metabolic rate and reducing the myocardial oxygen requirement should be quite helpful.

Dr. Blalock and others in our group have continued to prefer an anastomosis between the subclavian branch of the innominate artery and the side of the pulmonary. In the last 80 attempted anastomoses of this type, difficulty because of a short subclavian was encountered in only four cases. In these an end-to-end anastomosis was carried out successfully.

It should be emphasized that extensive mobilization of the systemic, as well as the pulmonary, vessels should be carried out if the subclavian branch of the innominate is going to be used.

We feel that a more accurate approximation of the intimal surfaces can be made when the subclavian is used than by using a thick-walled vessel such as the aorta. Since the innominate is on the right in about 80 per cent of the cases, the incision is usually made on the right. However, in some of the larger and older patients, and in some infants, we make the incision on the left and do an anastomosis either between the subclavian branch of the aorta and the pulmonary or use the aorta itself.

When the pulmonary is very small it is our feeling that an end-to-end anastomosis is technically superior to an end-to-side anastomosis between the subclavian and pulmonary, or a side-to-side anastomosis using the aorta. With increasing experience it becomes more apparent that one should be prepared to perform the anastomosis that is best suited to the anatomical relations of the vessels encountered at operation.

DR. EGBERT H. FELL, Chicago. At the Cook County Children's and Presbyterian Hospitals in Chicago, in the past year we have performed 20 operations on 18 children. In this group of 20 operations, ten were performed on children of two years of age or less. Five of the group were between four months and one year. There were two deaths.

in this group, both of them died of thromboses. We were encouraged to attempt surgery on a still smaller or younger age group, because it has been brought out numerous times that the mortality rate is greatest in the first year of life.

We were presented with three infants very severely cyanotic, requiring constant oxygen, food parenterally, and in a semi-comatose condition. The youngest was seven and one-half weeks, weighing seven lbs., the second was ten weeks old, weighing nine lbs., the third five and one-half months, weighing eight lbs.

(Slide) These three cases were diagnosed by Dr. B. M. Gasul, the cardiologist and pediatrician on our service, as tricuspid atresia or non-functional right ventricle. The fundamental problem is the same as that in the tetralogy of Fallot in the fact that there is an insufficient supply of blood reaching the lung. Therefore, the problem existed of making an artificial ductus, thus shunting blood to the lung.

Life is dependent, in cases of non-functioning right ventricle, upon an interauricular septal defect and a patent ductus arteriosus, and as long as the patent ductus stays open the child exists. As the ductus closes, the severity of the condition increases. We knew that if surgery was not done these three children would not survive.

We attempted the Potts-Smith procedure, the aortic-pulmonary anastomosis in all three cases, and we were pleasantly surprised that they were all benefitted. The seven and one-half-week-old child is now over eight months old, the ten-week-old child has survived over two and one-half months, and the five and one-half-month-old child lived over six and one-half months and was brought up from southern Illinois with a severe bilateral bronchial pneumonia and died within a few hours of admission.

(Slide) This shows the right heart. You see the interauricular septal defect. There is no indication of the tricuspid valve.

(Slide) This is a very small non-functioning right ventricle. There is no communication between the left ventricle or the right auricle with the right ventricle. The pulmonary artery leads from this rudimentary structure and is small. Note the marked hypertrophy of the left ventricle.

(Slide) This is what is left of the ductus, a very small probe can be introduced into it. It is non-functioning.

(Slide) This is the left heart showing a marked hypertrophy of the left ventricle and the interauricular septal defect.

(Slide) This is the orifice of the artificial ductus as seen from the aortic side, showing that it was patent, smooth, well healed and apparently functioning well, and there was no evidence of cardiac strain or that death was due to any cardiac involvement.

We feel that these procedures should be attempted on the severely ill individuals, and that Dr. Potts and Dr. Smith have contributed a great deal to the chapter which was so well begun by Dr. Blalock.

DR. ROBERT M. JANES, Toronto. Mr. President and Members: When I read the most interesting second paragraph in the summary of this paper, it occurred to me that perhaps Dr. Potts and you would like to know something of some experimental work that has been under way in our laboratory under the direction of Dr. W. G. Bigelow for the last year and a half. The work will be presented by Dr. Bigelow in the near future, and will be published in one of the scientific journals, so I do not want to unduly steal his fire.

However, he has been good enough to loan me a few slides which show very nicely the relationship that exists between oxygen consumption and temperature.

(Slide) This slide shows graphically the relationship that exists between the oxygen consumption, as shown on the left-hand side of the graph, and cooling and rewarming, the one line being the cooling and the other the rewarming. There isn't any doubt about the fact that this oxygen consumption does fall in definite relation to the fall in temperature. The temperature you see in centigrade at the bottom.

(Slide) This is a composite graph of all dogs during the process of cooling. You will see that it follows a fairly definite pattern.

(Slide) This is a graph of the dogs again in the process of rewarming.

(Slide) One of the factors that has introduced variables in work in the past is shivering. This slide shows the increased oxygen consumption that occurs in the first place to a slight shivering, and in the second to marked shivering. It is only one of the factors that may enter into and spoil the results of these experiments, which otherwise follow a very careful pattern.

Dr. Bigelow, of course, is interested in the application of these findings to the type of surgery that Dr. Potts has been talking about, it is also applicable to studies on survival.

DR WILLIS J POTTS, Chicago: Because of rather poor timing, I had to hurry over our mortality statistics. What I aimed to emphasize was that operative mortality depends upon a number of factors: choice of patients, age and coincidence, or more frankly, on runs of good or bad luck. During the terrible month of February 1948, our mortality was 50 per cent. During the past five months, there has been no mortality in a continuous series of 41 patients in the surgery of pulmonary stenosis. Operative mortality follows a surgeon like a shadow.

Assuming that no patient who has any chance of being relieved of cyanosis is refused operation, the mortality in all patients from infancy up to 16 years of age in whom a shunting operation is possible should be 10 per cent or less in a reasonably large series. In children between 3 and 16 years of age the mortality should be 5 per cent or below. In children below 3 years of age, the material is poor, the risk is great and the mortality will be high.

The most commonly asked question is this: "How large should the anastomotic channel between the aorta and the pulmonary artery be made?" A certain answer is still impossible. We now routinely make the incisions in the aorta and pulmonary artery, measured with a caliper $\frac{3}{16}$ of an inch (6.3 mm) long. These provide a final opening after suture approximately 4 mm in diameter. Originally we made the incisions $\frac{1}{4}$ of an inch (8 mm) long, but since the smaller incisions give just as good results, of course, for protection of the heart muscle, we use the smaller incisions.

AN EXPERIMENTAL EVALUATION OF CERTAIN METHODS OF SUTURING THE THORACIC AORTA*

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CONSIDERABLE IMPETUS has been lent to vascular surgery in recent years through its successful application to an increasing number and variety of clinical problems. In particular, corrective procedures, as well as those designed to meliorate incapacitating congenital cardiac anomalies have both kindled anew an interest in this field. The credit for these imaginative and provocative accomplishments is shared by Gross,¹ Blalock,² Crafoord,³ and Potts.⁴ Each has indicated a personal preference for a particular type of vascular anastomosis. Most of these variants on methods of suturing blood vessels were evolved before the turn of the last century.

In 1889 Jassinowsky⁵ reported his series of successful end-to-end anastomoses of carotid arteries of sheep, his fine silk sutures were interrupted, were placed one millimeter apart and pierced only the media and adventitia. In 1896 Jaboulay and Briaud⁶ reported their results on end-to-end blood vessel suture employing an everting continuous mattress stitch which permitted intima to intima approximation. Their early work on dog carotid arteries had numerous failures, but the same technic met with greater success on donkey carotid arteries, thus, early in the development of the field of vascular anastomoses the size of the vessel became recognized as an important factor determining a satisfactory end result. In 1897 Silverberg⁷ published the results of his studies. His anastomoses included all layers of the vessel. Without eversion the cut ends were united, using a continuous over and over stitch. The results were comparable to those of Jassinowsky, and Jaboulay and Briaud. It is evident that the basic methods employed currently in performing vascular anastomoses were developed and tested in the experimental animal before 1900. Other techniques of Murphy,⁸ Payr,⁹ and Lespinasse¹⁰ have, for the most part, been abandoned and are now mainly of historical interest. Carrel and Guthrie made several important contributions, particularly their method of triangulation, which facilitated blood vessel anastomoses.

Crafoord is reported to use a modification of methods first described by Silverberg and Jassinowsky, in which a continuous over-and-over silk stitch positioned to avoid piercing the intima, joins the vessels end to end. Gross,

* Work supported by grants from the Graduate School of the University of Minnesota and the Robert Ferguson Surgical Research Fund. Read before the American Surgical Association, St. Louis, Mo., April 20, 1949.

† Senior Research Fellow, U. S. Public Health Service.

‡ Associate Professor of Surgery, University of Washington, Seattle.

Blalock, Shumacher,¹² and others, favor the everting continuous silk mattress stitch apposing intima to intima, the suture technic identified with Jaboulay and Briau. Crafoord believes his method affords greater tensile strength at the suture line and permits an additional few millimeters wider resection on

TABLE I—*Materials and Methods of Suturing Used*

	6-0 Silk 27 anastomoses	5-0 Chromic 3 anastomoses	5-0 Plain 3 anastomoses
Continuous everting (mattress type)			
Continuous non-everting			
1 Through all layers	30	10	3
2 Through all layers (Excess intraluminal silk)	8		
3 Through media and adventitia only	4		

TABLE II—*Aortic Anastomosis Everting 6-0 Silk*

Dog No	P O Day	Leaking Sacri- Pressure in mm of Hg	Gross Findings
35E	1	210	Thrombus extending proximally and distally from suture line Size of thrombus 5 mm x 5 mm x 50 mm
51	2	305	Thrombus 4 mm x 5 mm x 60 mm extends distally and proximally
31E	3	340	No thrombus
29E	5	240	Very small flecks of fibrin along suture line
44	6	275	Large thrombus 5 mm x 4 mm x 50 mm
28E	6	Died of hemorrhage	Chest filled with blood clots 2 mm hole on back side suture pulled through
30E	7	Died of hemorrhage	Chest contain blood clots suture pulled through hole in aorta
25E	7	460	No thrombus
47	7	Died of hemorrhage	Suture apparently pulled through on both sides
36	7	270	Chest wound infected Small thrombus 2 mm in diameter
42	8	360	No thrombus
24E	9	358	Small thrombus just at anastomotic line
22E	10	Not tested	No thrombus Dog died of prolapse of recto sigmoid
56E	11	360	No thrombus
27E	11	390	No thrombus
26C	13	370	Small amount of thrombotic deposits along suture line
12B	14	190	No thrombus
34C	14	760 +	No thrombus
23E	20	520	Small thrombus 3 mm x 3 mm x 5 mm
49	20	280	No thrombus
32E	21	352	Thrombus 4 mm x 5 mm x 30 mm attached at suture line
21E	34	520	No thrombus
33E	46	510	No thrombus sutures pulling out small pits where sutures pulled out
52C	54	450	No thrombus wall of vessel at anastomosis show pits where sutures have pulled through
52	180	Not tested	No thrombus suture pulling out pits in intima
52 (Reop)	180	600 +	No thrombus sutures pulling out pits in intima
50	180	600 +	No thrombus sutures pulling out leaving small pits in intima

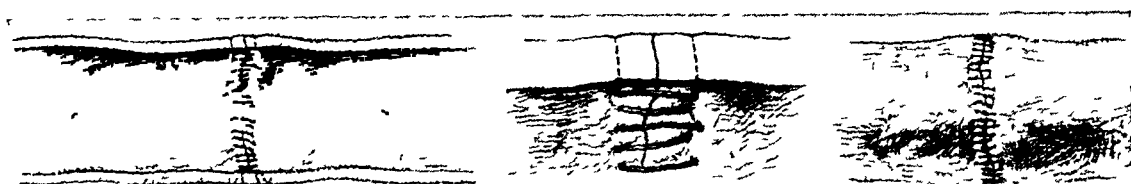
each side of the coarcted segment, but concedes that these benefits are associated with the development in some cases of a dissecting aneurysm. Gross and others, on the other hand, are convinced that the everting stitch minimizes the complications of both early hemorrhage and late aneurysm formation.

Potts' use of the non-everting suture method stems somewhat from the local anatomic technical considerations posed by his clamp

THE PROBLEM

In view of the conflicting opinions regarding the merits of the different methods of suturing the thoracic aorta after resecting areas of coarctation, this study was undertaken in an effort to shed some light on the experimental features of this problem

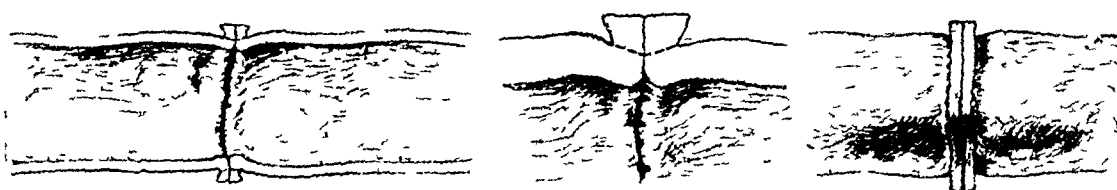
Available information, and generalizations from it, on blood vessel anastomoses of the carotid artery, femoral artery and abdominal aorta appear to be inapplicable to the thoracic aorta where the combination of blood vessel size, stresses on the vessel wall, and the turbulence of blood flow through the arch



End-on coaptation with suture through all layers



End-on coaptation with suture avoiding intima



Eversion with mattress suture

FIG 1—Methods of suturing the thoracic aorta

is unique. For this reason these experiments were conducted on the thoracic aorta. The animals used were dogs and these were observed up to one year following surgery. Physiologic and pathologic studies were carried out in an attempt to evaluate the relative merits of the various technics.

EXPERIMENTAL TECHNIC

Eighty-five mongrel dogs, ranging from 5 to 15 Kg in weight, were studied. Sodium pentobarbital was administered intravenously for general anesthesia, 30 mg per Kg being given initially. An intra-tracheal tube was inserted and a pneumatic cuff inflated. Respirations were maintained with

intermittent positive pressure while pure oxygen was delivered from a tank into a closed circuit. After preliminary surgical skin preparation, the left chest was entered through the fifth intercostal space. Satisfactory exposure of the upper thoracic aorta was uniformly obtained without rib resection. With the left lung partially collapsed the parietal pleura over the aorta was dissected free and preserved. No attempt was made to clear all the adventitia from the aorta as is conventionally done with smaller artery anastomoses. Care was taken to avoid damage to the thoracic duct. In about one-third of the animals the first pair of intercostal vessels was doubly ligated

TABLE III—*End-on Coaptation with 6-0 Silk Sutures Through All Layers*

Dog No	P O Day	Leaking Sacri- Pressure in ficed mm of Hg	Gross Findings
42A	1	310	Almost complete occlusion of aorta with a clot starting at suture line. Dog paralyzed in hindquarters
36A	3	450	No thrombus
56A	3	400	Large thrombus 8 mm x 20 mm from suture line
45	3	490	Small fibrin thrombus at suture line 5 mm x 2 mm x 2 mm
7A	3	550	Very small thrombus
49A	4	460	Very small amount of fibrin in suture line
4A	5	355	No thrombus
5A	6	460	No thrombus
2A	6	410	No thrombus
1A	7	400	No thrombus
37A	8	370	Small fleck of fibrin and red cells at suture line
48A	9	345	Thrombus on posterior wall 5 mm x 3 mm x 20 mm
39A	9	Not tested	Empyema thrombus 4 mm x 4 mm x 15 mm from suture line
53	10	440	No thrombus
55A	11	460	No thrombus
9A	13	Hemorrhage	Hemorrhage through anastomotic line one stitch seems to have missed catching all layers
12A	14	310	Thrombus present 5 mm x 5 mm x 15 mm from suture line
38A	14	420	No thrombus
6A	14	330	No thrombus
26A	17	490	No thrombus
8A	18	760 +	No thrombus
13A	20	740	No thrombus
80A	21	No leak at 600	Thrombus 4 mm x 3 mm x 3 mm from suture line
11A	55	690	No thrombus
79A	60	600 +	No thrombus
34	72	No leak at 740	No thrombus
52	180	Not tested	No thrombus
52 (Reop)	180	No leak at 760	No thrombus
10A	365	Not tested	No thrombus
3A	365	760 +	2 mm x 3 mm x 3 mm well organized and firmly adherent to vessel

and divided. The distal aortic arch and the proximal thoracic aorta were freed and mobilized. Specially modified intestinal clamps were applied across the aorta and the vessel divided. In some animals a segment varying from one to two centimeters in length was removed before doing the anastomosis, this was largely from the group in which intercostal vessels were divided. Suturing was usually started from the posterior portion of the vessel and was continued around anteriorly.

Eight series of experiments were conducted. Three different types of suture materials were employed: 6-0 braided silk,* 5-0 medium chromic catgut,† and 5-0 plain catgut ‡. All materials were swaged onto three-eighths curved fine, atraumatic, Kalt needles. Three different methods of suturing were employed, these are illustrated in Figure 1. Table I indicates the number of dogs handled in the varying manners.

Series I consisted of 26 dogs‡ in which the severed ends of the aorta were joined with a continuous everting mattress stitch of 6-0 braided silk. Sutures were placed one and a half millimeters from the vessel edge and one and a half millimeters between the return loops of the mattress suture. All of these were anchored by ligation at the midpoint.

Series II consisted of 29‡ dogs in which the severed ends of the aorta were anastomosed with a continuous, non-everting, over-and-over stitch of 6-0 braided silk which passed through all layers of the aorta-intima, media and adventitia. These sutures were placed one to one and a half millimeters from the cut edge and were one millimeter apart. In most instances a single strand was employed to sew the entire vessel while in a few the suture was anchored by ligation at the midpoint.

Series III consisted of eight dogs, in which a continuous non-everting anastomosis was done, employing 6-0 braided silk. The suture material passed through all layers of the aorta, but stitches were placed approximately two and one-half millimeters from the cut edge. By such means excessive amounts of silk were deliberately exposed in the lumen. The distance between sutures was the same as in Series II.

Series IV consisted of four dogs, in which a continuous non-everting anastomosis was performed, employing 6-0 braided silk. Here the suture material passed through only the media and adventitia and the point of entrance of the suture into the vessel wall was two and one-half millimeters from the vessel's cut edge.

Series V and VI consisted of 3 and 10 dogs respectively. 5-0 medium chromic catgut was employed. Stitching was done the same as in Series I and II respectively.

Series VII and VIII consisted of three dogs each. In these experiments 5-0 plain catgut was used and again stitching was done in the same manner as in Series I and II respectively.

Following the completion of the anastomosis the clamps were removed rapidly, first the distal and then the proximal clamp. There was uniformly an acceleration of the heart rate upon the rapid removal of the clamps, but no other ill effects were noted. Bleeding from the operative suture line was infrequent regardless of the method used. In an occasional instance after removal of the clamps, blood pumped out through the suture line. Cessation

* Average tensile strength found to be 410 Gm

† Average tensile strength found to be 560 Gm. This and the above were supplied through the courtesy of Johnson and Johnson, New Brunswick, N. J.

‡ One animal was operated upon more than once.

FIG 2

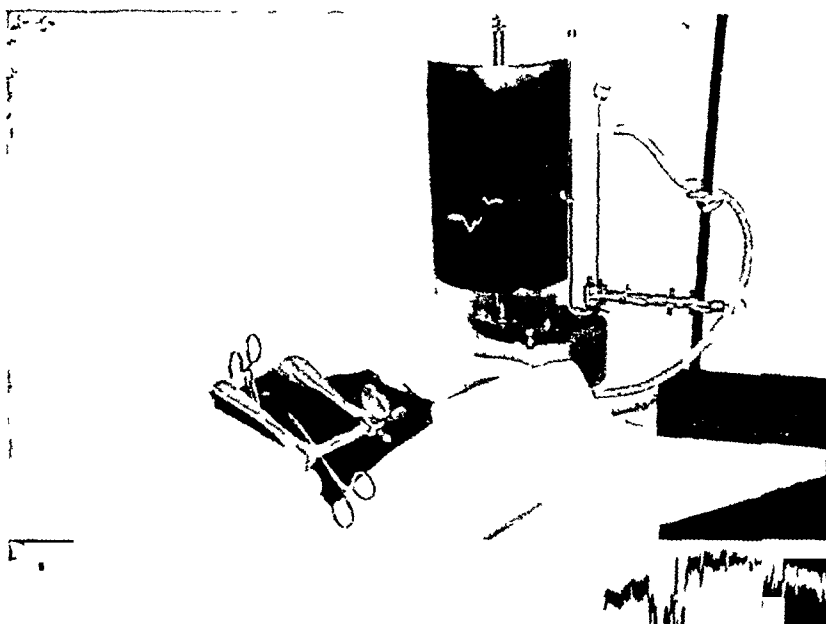


FIG 3

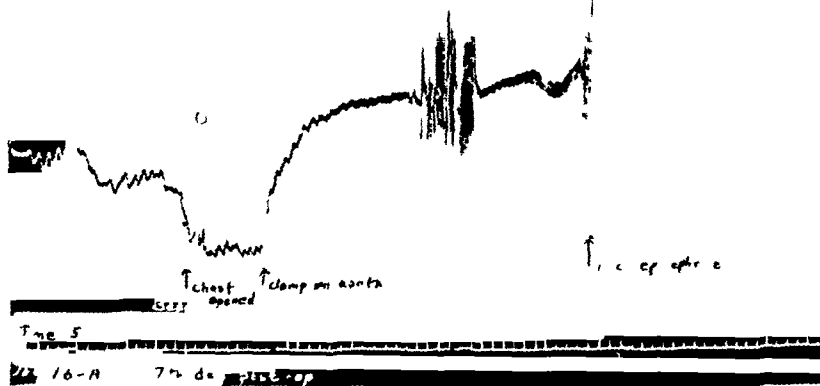


FIG 4

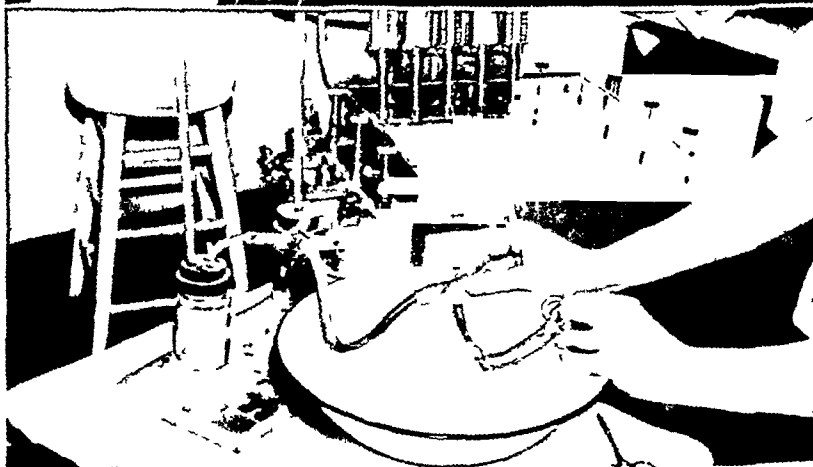


FIG 2—Apparatus for measuring intraluminal pressure in situ

FIG 3—Reproduction of kymographic tracing. Maximal pressure of 350 mm of Hg was obtained

FIG 4—Apparatus for measuring maximal intraluminal pressure tolerated by the aorta

SUTURING THE THORACIC AORTA

of this hemorrhage occurred regularly after mild pressure was patiently maintained over the bleeding point with a finger and moist gauze for three to five minutes. The anastomotic site was in all instances carefully pleuralized. Pericostal sutures were placed, the lungs fully expanded, and the chest wall muscles then closed in layers. Postoperatively the dogs recovered in their cages, soon resumed full activity, and ate regular kennel diet. In no instance were anticoagulants administered pre- or postoperatively.

Complications as a direct result of surgery included empyema, paralysis of the hind legs, and hemorrhage at the anastomosis. Early in the experiments a suppurative pleuritis occurred in about one-third of the animals. The subsequent routine instillation of 50,000 units of penicillin into the pleural space eliminated this complication. Paralysis, transient or permanent, of the lower

TABLE IV—*End-on Coaptation with 6-0 Silk Suture Avoiding Intima*

Dog No	P O Day Leaking		Gross Findings
	Sacri- ficed	Pressure in mm of Hg	
50A	3	270	Very small thrombi started from intimal edge 2 mm x 3 mm x 16 mm
78A	6	310	No thrombus
51A	14	450+	Died of distemper No thrombus
53A	50	No leak at 450	No thrombus

TABLE V—*End-on Coaptation with Excess Silk in Lumen*

Dog No	P O Day Leaking		Gross Findings
	Sacri- ficed	Pressure in mm of Hg	
45A	6 hrs	240	Cause of death indeterminate Small fibrinous deposits around sutures
49A	4	460	Small thrombus 2 mm x 3 mm along sutures
47A	6	320	Small thrombotic deposits along sutures
48A	9	345	Large thrombus fills lumen of vessel
43A	13	No leak at 680	Empyema Only small thrombi around sutures
46A	17	380	No thrombus
44A	21	420	Small thrombus 2 mm x 3 mm x 3 mm
54A	30	No leak at 450	No thrombus

limbs, along with bladder and rectal sphincter dysfunction, occurred, especially in older dogs, when the aorta was clamped for longer than 25 minutes. With an increasing experience most anastomoses were accomplished in about 15 to 18 minutes. The animals which died on the table from immediate intra-thoracic hemorrhage have been omitted from this series, such hemorrhages were primarily the result of faulty operative technic, and occurred in the earlier phases of the problem. Delayed hemorrhages will be discussed below.

The tensile strength of the healing or healed aorta was assayed at intervals ranging from one day to one year. At the onset a number of anastomoses were tested in situ (Figure 2). At such times the dogs were anesthetized with sodium pentobarbital, an intra-tracheal airway was inserted, respirations were

maintained with intermittent positive pressure, the carotid artery was cannulated for recording arterial pressures with a mercury manometer, and the left chest was opened without sterile technic. The anastomotic site was observed. A basal blood pressure reading was obtained. The aorta was cross clamped distal to the anastomosis and blood pressure tracings secured. Subsequently, 1 cc of 1 to 1000 epinephrine was injected into the left auricular appendage and repeated blood pressure tracings were recorded (Figure 3). Arterial blood pressures as high as 350 mm of mercury were obtained in this manner and in only one instance* did bleeding from the suture line follow such an examination.

Finally the distal aortic arch and thoracic aorta were excised together, one end of the aorta was cannulated, and the other clamped (Figure 4), and with the specimen under water the sutured ends gradually distended with compressed air until the first leak was noted. This value was measured with a mercury manometer. The vessels were then opened and photographs taken. The character of the intraluminal surface of the anastomosis was noted, with special attention directed to the presence or absence of thrombi. Appropriate sections for microscopic examination were fixed in 10 per cent formalin. These were stained with hematoxylin and eosin and van Gieson's stain.

EXPERIMENTS

Tables II to IX summarize the results of 88 satisfactory protocols in the eight series of experiments. This is graphically represented in Figures 5 to 8. Detailed consideration is given below to (1) the intraluminal pressures tolerated by sutured vessels, (2) the incidence of thrombus formation, (3) hemorrhage, (4) the fate of the suture line, (5) the gross pathology, and (6) the microscopic pathology.

1 *Intraluminal pressures tolerated by sutured vessels* When 6-0 braided silk and 5-0 medium chromic catgut were employed as the suture material, irrespective of the stitching technic, all sutured vessels withstood intraluminal pressures in excess of physiological needs. When 5-0 plain catgut was employed, on the other hand, with an everting mattress stitch dehiscence was inclined to occur within the first week after the anastomosis was performed.

The endpoint in testing for leakage was that level of air pressure, measured in millimeters of mercury, at which juxta-anastomotic bubbles or sub-adventitial blebs of air were visible. Although in some instances it was difficult to determine from whence the leak occurred, in most tests air appeared to emerge from the point of penetration of a suture. In no instance was leakage noted along the apposed tissue margin of the cut ends of the anastomosed area, nor did enormous or total dehiscence occur under the conditions of this examination.

2 *The incidence of thrombus formation* In reporting the presence or absence of thrombi complete objectivity was adhered to regardless of any investigator's impression as to its potential clinical significance. The slightest evidence of thrombus formation, be it only a one-millimeter-in-diameter

* This occurred at 270 mm of mercury on the seventh postoperative day.

FIG 5

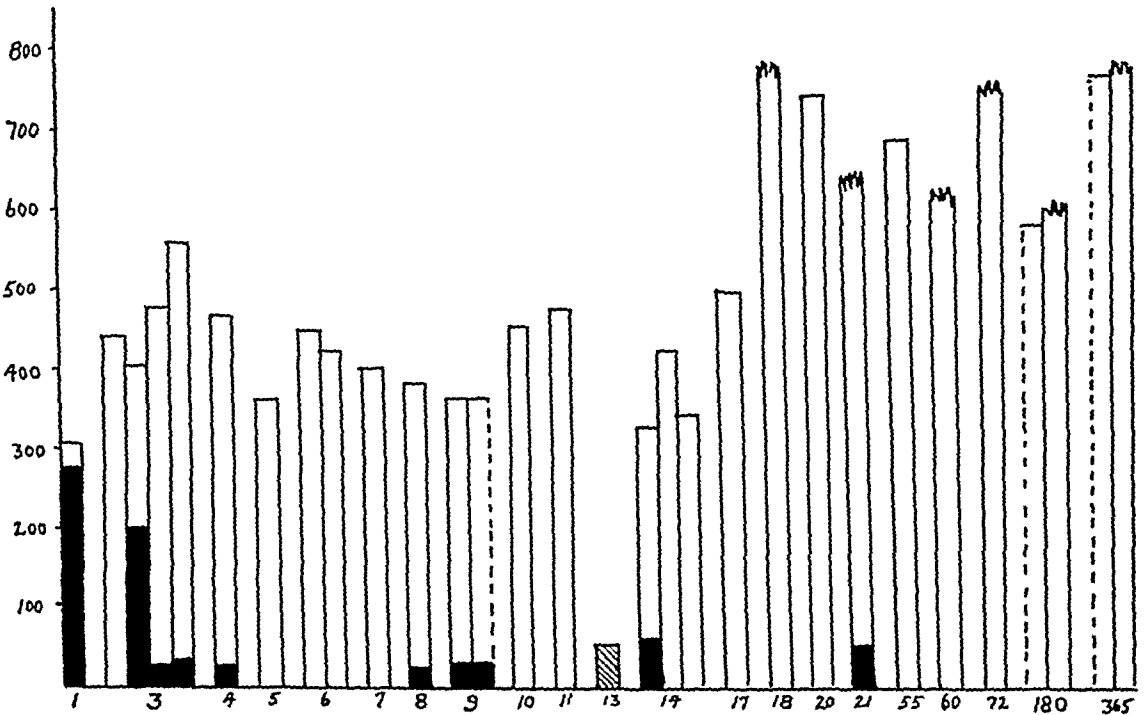
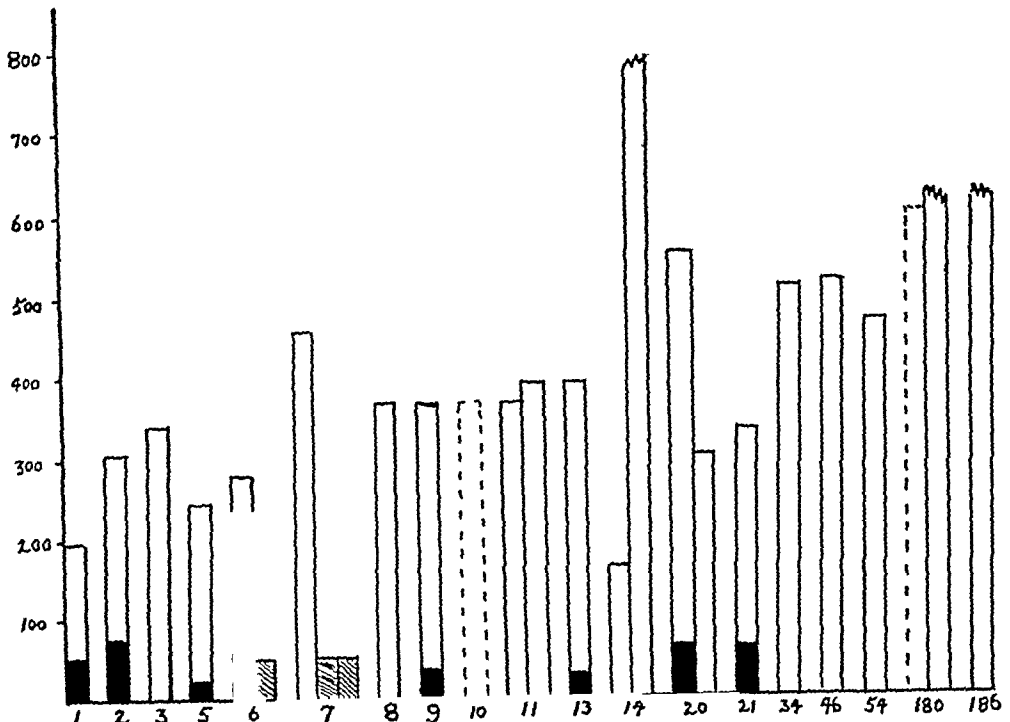


FIG 6

FIG 5—Eversion type mattress suture with 6-0 silk. Numbers represent postoperative days. Each bar represents one anastomosis and pressure withstood. Shaded area represents occurrence and estimate of size of thrombus. Broken bar represents maximal pressure not determined. Diagonally lined bars represent hemorrhage. Dotted line bars indicate specimen not tested.

FIG 6—Continuous end-on coaptation suture through all layers with 6-0 silk. Numbers represent postoperative days. Each bar represents one anastomosis and pressure withstood. Shaded area represents occurrence and estimate of size of thrombus. Broken bar represents maximal pressure not determined. Diagonally lined bars represent hemorrhage. Dotted line bars indicate specimen not tested.

FIG 7

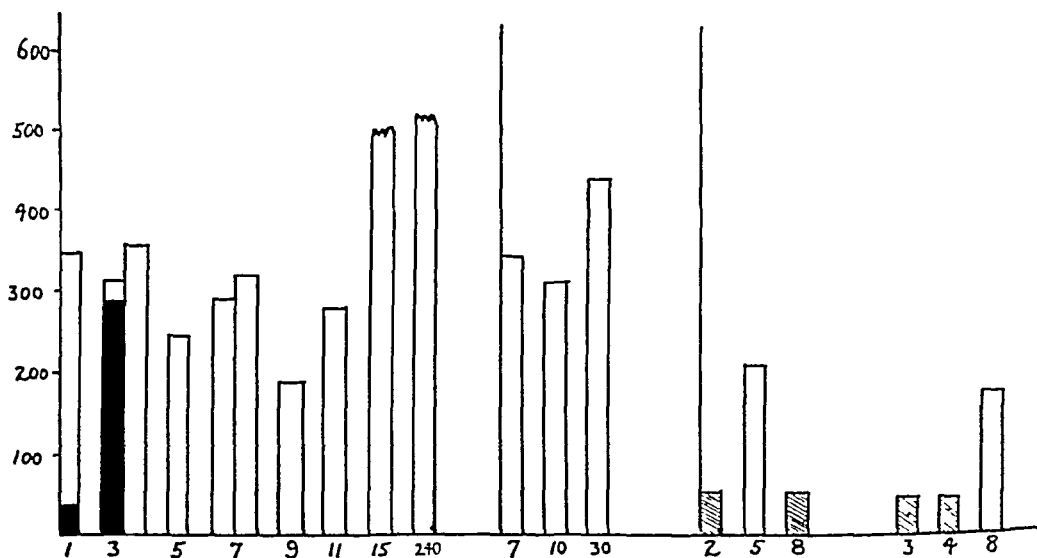
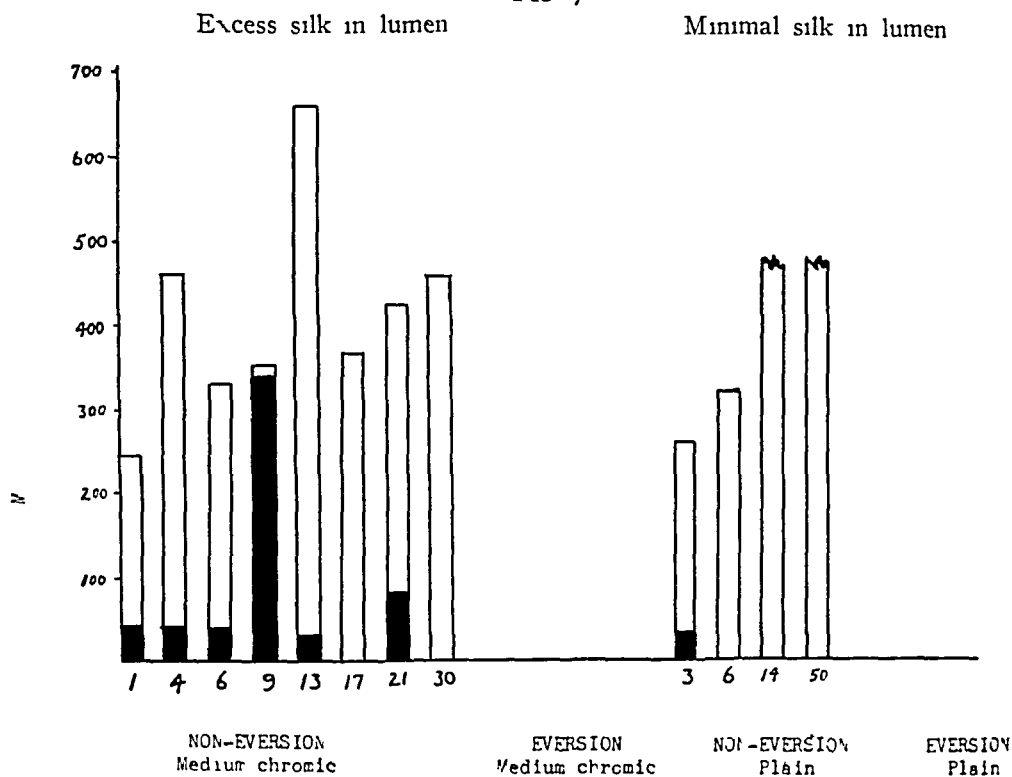


FIG 8

FIG 7—End-on coaptation with 6-0 silk suture avoiding intima and with excess silk in the lumen. Numbers indicate postoperative days. Each bar represents one anastomosis and pressure withstood. Shaded area represents occurrence and estimate of size of thrombus. Broken bar indicates maximal pressure not determined.

FIG 8—Anastomosis with 5-0 medium chromic catgut and 5-0 plain catgut. Numbers represent postoperative days. Each bar represents one anastomosis and pressure withstood. Shaded areas represent occurrence and estimate of size of thrombus. Diagonally lined bar represents hemorrhage.

accumulation of fibrin beneath or close to a suture, was tabulated positively (Figure 9) It is of interest to note that in only two instances were thrombi large enough to fill an entire vessel lumen

In 30 non-everting, end-on anastomoses made with 6-0 braided silk taken through all layers of the vessel wall at one millimeter distance from the cut

FIG 9



FIG 9A

FIG 9—End-on coaptation through all layers with silk Two weeks
FIG 9A—Photomicrograph of specimen shown in Fig 9 $\times 30$

ends, there were four minute thrombi consisting of a mere fleck of fibrin, six instances of small to medium sized thrombi, and a large sized one in which the vessel lumen was occluded In 26 everting anastomoses made with

6-0 braided silk there were seven specimens with small to medium sized thrombi and an additional three displaying only tiny fibrin flecks. In the eight dogs with non-everting end-on anastomoses, and with the silk placed two and a half millimeters from the cut edges to expose more silk in the lumen, there was one specimen with a medium sized thrombus (Figure 15) and three others which had minimal thrombotic deposits. Little or no silk was exposed in the lumen of four dogs in which stitches were taken through only the media and adventitia, only one of these four animals exhibited a tiny fleck of fibrin.

In the ten non-everting end-on anastomoses, made with 5-0 medium chromic catgut, there was one specimen with a medium sized thrombus and one with an enormous thrombus completely occluding the lumen. In no other experiment was there thrombus formation.

TABLE VI—*End-on Coaptation with 5-0 Medium Chromic Catgut Through All Layers*

Dog No	P O Day Leaking		Gross Findings
	Sacri- ficed	Pressure in mm of Hg	
21A	1	340	Small thrombus consisting of fibrin strands along one part of suture line
52	3	310	Thrombus 2 cm long completely filled lumen of vessel
20A	3	358	No thrombus
19A	5	230	No thrombus
16A	7	290	No thrombus
17A	7	320	No thrombus
16A	9	190	No thrombus
18A	11	290	No thrombus
15A	75	No leak at 500	No thrombus
14A	240	No leak at 500	No thrombus

TABLE VII—*End-on Coaptation with 5-0 Plain Catgut Through All Layers*

Dog	P O Day Leaking		Gross Findings
	Sacri- ficed	Pressure in mm of Hg	
62A	7	340	No thrombus
61A	10	310	No thrombus
54A	30	No leak at 450	No thrombus

Thrombi forming during the first eight postoperative days, whether small, medium, or large, were soft and friable. Thrombi in animals surviving for longer periods of time were progressively firmer, and less easily dislocated. The thrombus shown in Figure 11 was discovered one year following the anastomosis, measured 10 x 5 x 3 mm and had become an integral part of the vessel wall. In three instances unusual thrombi extended not only distally from the anastomotic line, but also several centimeters proximally into the subclavian artery.

No dog at any time displayed evidence of embolization clinically or at autopsy.



FIG 11A

FIG 10A —Photomicrograph of specimen shown in Fig 10 $\times 30$
 FIG 11A —Photomicrograph of specimen shown in Fig 11 $\times 30$



FIG 11

FIG 10 —End-on coaptation through all layers with silk Eight weeks
 FIG 11 —End-on coaptation through all layers with silk One year

3 *Hemorrhage* Very little difficulty was encountered with acute blood loss at the time of surgery after some technical familiarity was acquired. When fatal hemorrhage occurred on the table (and it did in our early experience) these protocols have been omitted from this report. Rarely, a small leak resulted from a single untightened or misplaced stitch that failed to seal after five minutes of gentle pressure. In such instances the error was readily corrected by an additional interrupted suture. Even when stitches were properly placed an occasional spurt of blood emerged at the site of penetration of the needle, such bleeding consistently stopped in a few minutes with gentle digital pressure. Immediate hemorrhage did not appear in any way to be related to the type of suture material or the stitching technic.

TABLE VIII—*Evercion with 5-0 Medium Chromic Catgut*

Dog No	P O Day Leaking		Gross Findings
	Sacri- ficed	Pressure in mm of Hg	
67E	2	Died of hemorrhage	No thrombus
19A	5	230	No thrombus
57E	8	Died of hemorrhage	Gross dehiscence

TABLE IX—*Evercion with 5-0 Plain Catgut*

Dog No	P O Day Leaking		Gross Findings
	Sacri- ficed	Pressure in mm of Hg	
64E	3	Hemorrhage	Gross dehiscence
66E	4	Hemorrhage	Gross dehiscence
65E	8	220	No thrombus

For the most part delayed hemorrhage presented no serious problem. One instance of hemorrhage was encountered in a non-everting end-on anastomosis using silk. This animal died on the 13th postoperative day and examination of the specimen showed that at least one loop of the suture was improperly placed. In silk anastomoses performed with an everting stitch three fatal hemorrhages occurred—one on the sixth and two on the seventh postoperative days. In all three instances a loop of silk was noted to have pulled through the vessel, resulting in a focal dehiscence with hemorrhage.

With 5-0 chromic and 5-0 plain catgut sutures employing a non-everting end-on stitch no hemorrhage occurred. With an everting technic, on the contrary, fatal bleeding episodes were noted. Of three dogs sewed with 5-0 chromic catgut one bled on the eighth postoperative day, of three dogs sutured with 5-0 plain catgut one exsanguinated on the third and another on the fourth postoperative days. In the first instance one loop of mattress stitching pulled through and in the last two the suture material gave way and the vessels pulled apart completely.

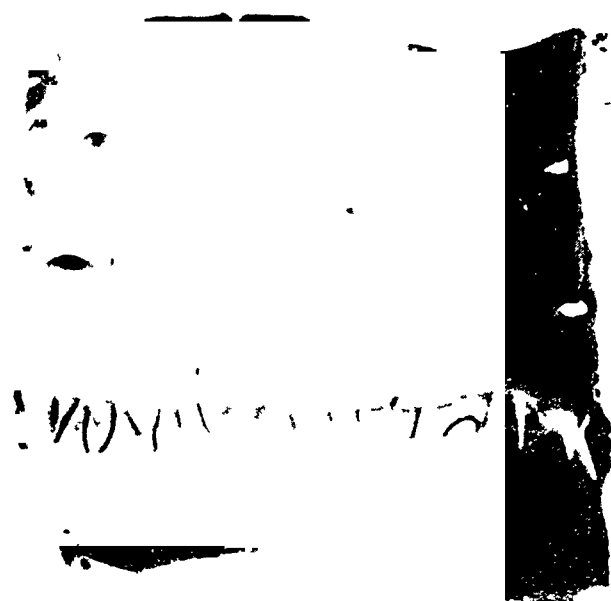
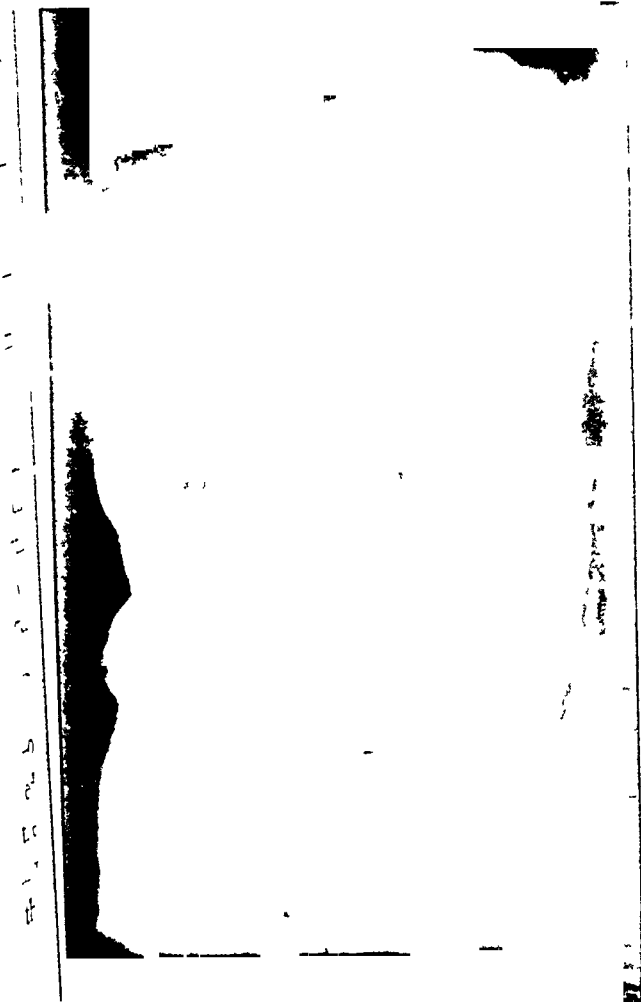


FIG 13

FIG 12—Everson with mattress type silk suture Two weeks
FIG 13—Everson with mattress type silk suture Eight weeks



FIG 13A

FIG 12A—Photomicrograph of specimen shown in FIG 12 x 30
FIG 13A—Photomicrograph of specimen shown in FIG 13 x 30

4 *The fate of the suture material* In every vessel, sewed end-on with silk and without eversion, the suture material remained intact, up to periods of one year (Figure 11) In several vessels united by silk and with eversion, individual loops of the suture were noted to have pulled through (Figures 13, 14)—a process that appears to continue throughout the late weeks and months of recovery as the eversion straightens out and the vascular fibers realign In all instances in which the animals survived, the silk had become covered by a thin layer of endothelial cells as early as 10 to 16 days postoperatively Of the 12 animals anastomosed with medium chromic catgut the suture material remained grossly visible up to 30 days, but none was recognizable after two months

5 *The gross pathology* When cylinders of the aorta, including the area of the anastomosis, were removed the site of suturing was usually surrounded by heaped up adventitia Once this was carefully trimmed away a



FIG 14—Specimen showing two lateral anastomoses made with end-on coaptation suture through all layers, central anastomosis made with everting mattress type suture Six months

slight stenosis was observed Anastomoses which were performed a year previously on small puppies displayed a retarded growth compared with the adjacent vessel In no experiments, however, had the outside diameter become lessened with the passage of time There was little difference in the external appearance of specimens sutured several months earlier by various methods and with different materials

After opening the cylinders longitudinally the specimens were pinned on a board to facilitate careful scrutiny Vessels anastomosed with non-everting end-on silk sutures, taken through all layers, uniformly displayed a smooth intimal apposition (Figures 16, 17) When the intima was omitted from the suture a wider slit occurred between apposing intimal margins Vessels anastomosed with a continuous everting silk mattress suture con-

sistently displayed a more irregular apposition and a furrow occurred at the everted interface (Figure 12). With the passage of time postoperatively, the prominence of this sinuate track became less noticeable, but small pits regularly developed where mattress stitches had pulled through (Figures 13, 14). The smoothest endothelial surfaces were observed where non-everting catgut sutures were employed.

6 *The microscopic pathology* Reference to Figures 12A and 13A best demonstrate how the fibers of the media bend outwards in the early stages of repair where everting stitches were employed. After several months of healing these fibers gradually become realigned parallel with the long axis of the aorta. During such intervals of time the intervening cleft is filled with fibrin and proliferating intimal cells. Anastomoses performed with non-

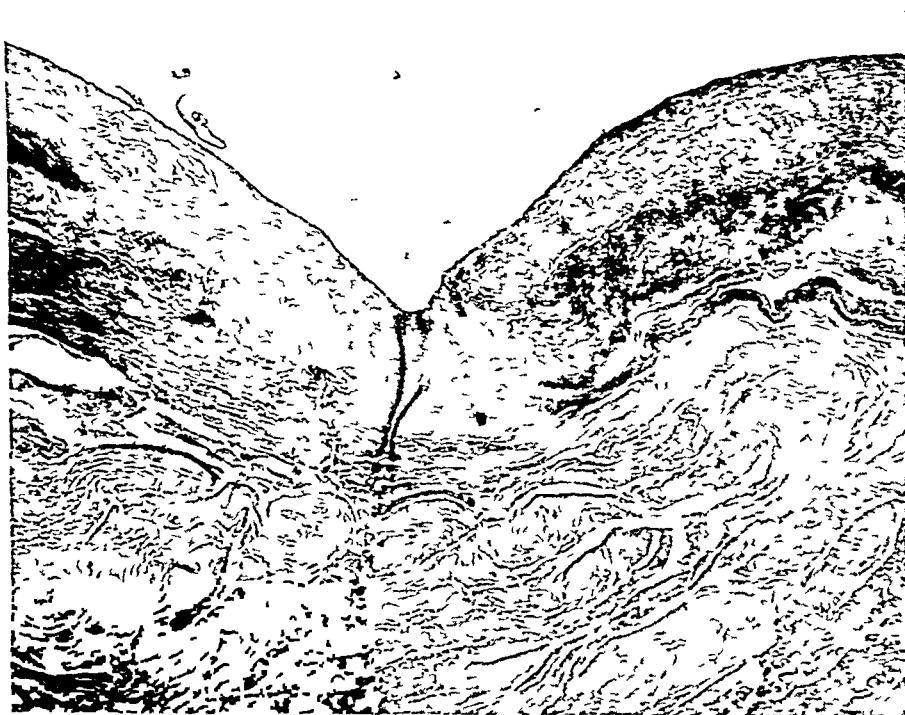


FIG 14A—Photomicrograph of middle anastomosis shown in Fig 14
x 30

everting end-on stitching, on the other hand, are anatomically aligned at once (Figure 10A), with final healing occurring earlier than after suturing with eversion. In all types of stitching the sutures become rapidly mesothelialized, and in a very few days these cells (Figures 9A and 12A) migrate across the fibrin base. Chromic catgut sutures are demonstrable in microscopic sections up to 60 days, but become largely fragmented, absorbed, and replaced with fibrous scar tissue soon thereafter.

DISCUSSION

This study suggests that in dogs the divided thoracic aorta, when united either with a continuous non-everting end-on whipping stitch or with an everting continuous mattress stitch, employing 6-0 braided silk, is consistently strong enough to withstand more than the physiological needs of the

animal As the severed aorta heals, the everting mattress stitch tends to pull through the vessel wall, the eversion tends to flatten out, and in this manner the longitudinal fibers realign Should the mattress loop of the suture pull through during the first seven days, fatal hemorrhages may occur If the sutures pull through later, the healing has usually progressed far enough so that no hemorrhage ensues, when, however, the suture has pulled through at a late stage foveolae or crypto-aneurysms are formed which result in an intraluminal irregularity of the endothelial lining As each anastomotic line was developed, a snug but in nowise strangulating tension was maintained on the laid sutures

The presence of intraluminal or subendothelial loops which have cut through, as well as imperfections of the aortic wall, may be related to other factors All anastomoses derive strength by the acceptance at numerous points of a fraction of the total strain This distribution of tension may be less equitable with the everting type than with the non-everting end-on whipping stitch including all layers In the former, focal areas might be compelled to accept a disproportionate share of the disrupting force Another possibility stems from the shearing action generated by each cardiac thrust which would ultimately saw through the segment of aortic wall captured by a particular loop of mattress suture Support for these theoretical considerations is provided by a special experiment designed to explore this problem further

In this dog an everting type mattress suture anastomosis was made after transection of the aorta Six months later this anastomosis was resected* removing 1 cm of aorta on each side of the anastomotic line An end-on anastomosis without eversion was made with an over-and-over whipping stitch of 6-0 silk through all layers Two weeks following this the dog was reoperated upon, the aorta divided distal to the anastomosis, and a fresh homo-graft 10 mm longer than the resected segment was inserted to bridge this defect The proximal anastomosis on the graft was effected with a 6-0 silk everting type of mattress suture and the distal anastomosis made with a 6-0 silk over-and-over whipping stitch including all layers Six months later the entire aorta was removed and examined As noted in Figure 14 the outside anastomoses are of the end-on whipping stitch variety, and the middle suture line is of the everting type There appears to be more evidence of dislocation in the latter (free loops and pitted walls) than in either of the other anastomoses, despite the fact that the proximal one was under considerably more tension At the time it was made, a 2 centimeter segment had just been excised whereas a 3 centimeter graft had just been added upon the occasion of the last procedure

That everting sutures suffer more from tension on the line of anastomoses was also demonstrated by a short series of experiments in which either a chromic or a plain catgut suture was employed The high incidence of fatal

* This anastomosis demonstrated free loops where the mattress stitching had pulled through

FIG 16



FIG 15



FIG 17A

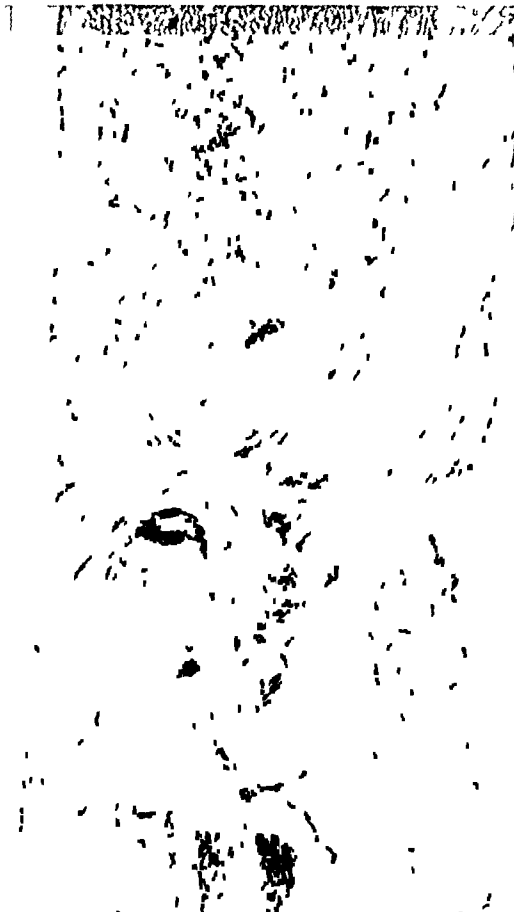


FIG 17

FIG 15—Medium sized thrombus in anastomosis made with excess silk exposed to the lumen Three days
FIG 16—End-on coaptation through all layers made with 5-0 medium chromic catgut One week
FIG 17—End-on coaptation with 5-0 medium chromic catgut through all layers 75 days
FIG 17A—Photomicrograph of specimen shown in FIG 17 x 30

hemorrhages in the catgut everted series (three out of six) compared with the end-on non-everting series (none), suggests that there are greater tension effects on the suture line with eversion. These experiments are, in a sense, peak load tests of healing capacity. But, since the usually encountered hyperpiesia is considerably below the pressure required to disrupt an everting type of anastomosis, any broad claims for superiority of the end-on whipping type stitch appear rather academic.

As far as thromboses are concerned these experiments corroborate the results of other workers: any irregularity in or on the vessel wall promotes thrombus formation. In our experience, this does not appear to be simply a question of the presence or absence of non-absorbable suture material. Smith⁴ has shown that if a fine silk suture is threaded transversely through an artery, tiny clots form in the center of the turbulent stream. These grow until the vessel becomes occluded. When a stitch is placed parallel with the longitudinal axis of the vessel, the foreign body hugs the intima, turbulence is minimal and few thrombi form. Examination of the specimens from this series of experiments suggests that the irregularities at the anastomotic line are probably as important in thrombus formation as the suture material used.

The incidence of thrombus formation along the anastomotic site in these experiments was nearly the same whether suturing was done with an everting or a non-everting stitch. Thrombus formation was infrequent when end-on stitching was carried out to include adventitia and media, but omitting the intima.

Catgut anastomoses have uniformly produced the smoothest end result when a non-everting end-on stitching was carried out. Yet, because of lower pressures at which leaking occurred in the early days of healing, catgut anastomoses offer a reduced margin of safety.

CONCLUSIONS

1 The severed thoracic aorta of the dog, united with 6-0 braided silk using an end-on whipping stitch or an everting mattress type of suture, has tensile strength in excess of the animal's physiologic needs.

2 When the eversion type of mattress sutures pulls through the vessel wall, irregularities develop on the endothelial surfaces and sometimes in the structure of the vessel wall.

3 A continuous 6-0 braided silk placed with a non-everting end-on coaptation stitch remains intact in vessels observed up to one year post-operatively.

4 There appears to be an equal incidence of thrombus formation in anastomoses made with over and over whipping stitch with 6-0 silk without eversion and in anastomoses made with 6-0 silk of the everting mattress type.

5 Intraluminal silk plays a small role in thrombus formation at the anastomotic line.

6 There was no instance in which the anastomosis became narrower than at the time of surgery. In anastomoses done on puppies, nevertheless it was

noted that growth at the site of suturing does not keep abreast of the growth of the adjacent aorta

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THE SURGICAL RELIEF OF CONGESTION IN THE PULMONARY CIRCULATION IN CASES OF SEVERE MITRAL STENOSIS*

PRELIMINARY REPORT OF SIX CASES TREATED BY MEANS OF ANASTOMOSIS
BETWEEN THE PULMONARY AND SYSTEMIC VENOUS SYSTEMS

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IT IS ESTIMATED that approximately ten per cent of patients with rheumatic disease of the mitral valve ultimately develop a preponderant degree of stenosis. Although such patients may not, at least for many years, experience any striking symptoms or suffer any great limitation of their activities, there are some who develop a syndrome which is characterized by the occurrence of attacks of pulmonary edema. These attacks are precipitated by the physiologic changes which occur during menstruation or pregnancy, intercurrent infections, fever, or tachycardia induced by emotional disturbances or marked increases in physical exertion. But for many years the heart itself may remain relatively normal save for slight enlargement.

The explanation for the phenomenon depends upon the concurrence of two factors. The first is that as a result of the long-standing mitral stenosis, a continuous increase in the pressure within the pulmonary circulation develops. With this increased pressure the characteristic congested condition of the lungs becomes established. The second factor is that the right ventricle ultimately becomes hypertrophied in response to the increased pressure in the pulmonary circuit. The result of this is that under conditions of stress the strong right ventricle forces blood into the lungs so as to increase greatly the already elevated pressure within the pulmonary vessels. This inevitably results under strain in the transudation of fluid and often of blood into the pulmonary alveoli, producing the clinical picture of pulmonary edema. After the stage of the disease is reached when attacks of pulmonary edema occur with frequency, the patient lives in jeopardy and is forced to adopt a program of very limited activity even though the heart muscle remains competent. Such patients often die of pulmonary failure rather than from failure of the heart itself.

The first attempts to relieve the effects of tight mitral stenosis were directed chiefly at the enlargement of the mitral opening. Originally this was done by dilating the stenosed orifice with a finger inserted through a small incision in the right ventricle. Later an effort was made by Cutler¹ and others to enlarge the opening by means of cutting instruments. These early attempts met with failure, and the experiences of others since then have been for the most part equally unsuccessful. Recently Harken² has modified the technic

* Read before the American Surgical Association, St Louis, Mo., April 20, 1949

of valvulotomy and has had somewhat better results. It must be kept in mind, however, that in addition to the rather considerable mortality risk of the procedure, the operation leaves the patient with an increase in the element of regurgitation which cannot be controlled. The unfavorable effects of this factor upon the heart muscle may lead to a disappointing end result.

The interesting observation first reported by Lutembacher,³ that patients with tight mitral stenosis who have a coexisting patent interauricular septal defect do not usually suffer from paroxysms of pulmonary edema, has led to the suggestion that such a defect might be created by surgical means. Blalock has begun to approach the problem from this angle and has published the details of his technic as utilized in experimental animals.⁴ This operation of course involves the serious risk of manipulations within the heart itself.

A clue to the possibility that a different approach to the problem of relieving the congestion within the pulmonary circulation may exist arises from the observation that in patients with tight mitral stenosis the bronchial veins become enormously dilated. This increase in the collateral bronchial venous circulation tends to provide an outlet, limited in extent to be sure, from the congested pulmonary vessels. This compensatory mechanism suggests that if a larger communication can be created between the pulmonary and the systemic venous systems, a more effective relief of sudden increments of pressure within the pulmonary circuit might be provided. Such a shunt, in addition to being an improvement upon nature's spontaneous efforts to create a collateral communication, would also have essentially the same effect upon the pressure in the congested area as that which results from the presence of an interauricular septal defect. It would, in fact, be essentially equivalent to the creation of a septal defect, but would have the advantage that it is an operation performed outside of the heart. The risk of intracardiac manipulation would thereby be avoided.

OPERATION—ANASTOMOSIS BETWEEN THE SUPERIOR SEGMENT[™] BRANCH OF THE RIGHT INFERIOR PULMONARY VEIN AND THE AZYGOS VEIN

Anatomical considerations. Two veins exist which are ideally suited for the creation of a shunt from the pulmonary to the systemic circulation. These are the superior segment branch of the right inferior pulmonary vein and the azygos vein. These veins lie close together and have approximately the same diameter. Furthermore, their direction is nearly enough parallel to make it easy to approximate them end-to-end after division. From the mechanical aspect also the release of pressure in the left auricle, which might result from an anastomosis between the cardiac end of the pulmonary vein and the cardiac end of the severed azygos vein, would seem to produce the desired effect upon the congestion in the lungs (Fig. 1).

The azygos vein arises over the bodies of the upper lumbar vertebrae and enters the thorax through the aortic hiatus in the diaphragm. It passes along

the right side of the vertebral column to the level of the fourth thoracic vertebra where it arches forward over the right main bronchus to enter the superior vena cava. In its course it lies near the esophagus and next to the thoracic duct. It is joined by the hemiazygos and accessory hemiazygos veins, the right intercostal veins, the right highest intercostal vein, the esophageal, mediastinal, and pericardial veins, and the right bronchial vein. Its diameter varies from 2 to 3 millimeters at its lower end to 6 or 7 millimeters or more at its termination in the superior vena cava. There are, of course, variations in size from one person to another. The superior segment branch of the right inferior pulmonary vein arises in the superior segment of the right lower lobe behind the corresponding segmental bronchus. During its short course before it joins the veins from the basal segments of the lower lobe to form the

inferior pulmonary vein, it receives several small branches, some of which may enter it close to its termination. Occasionally the superior segmental vein enters the left auricle independently of the inferior pulmonary vein as a separate trunk. Its diameter varies from approximately 3 to 5 millimeters. In patients with mitral stenosis this vein, in company with all the pulmonary veins, is somewhat larger in diameter than normal and unusually turgid because of the increased pressure in the left auricle. It is thin-walled, however, and corresponds in this respect with the azygos vein to which it is to be anastomosed.

Special Precautions To Be Observed Because of the danger of inducing an attack of pulmonary con-

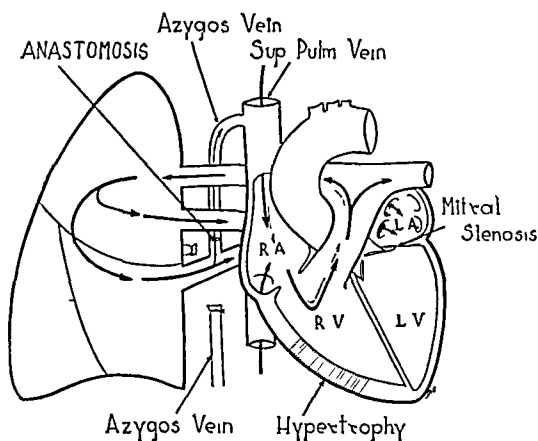


FIG 1—Pulmonary-azygos venous shunt. Schematic diagram to show the mechanical effect of a shunt between the pulmonary and the systemic venous circulations produced by an anastomosis between the azygos vein and the right inferior pulmonary vein. Arrow shows that some of the blood in the inferior pulmonary vein is forced by the high pressure in the pulmonary circuit to enter the azygos vein through the shunt, thus relieving to some extent the excess of pulmonary pressure.

gestion as a result of excitement, the patient is put to sleep in his room by means of Pentothal injected intravenously. He is then moved to the operating room and the inhalation anesthesia is begun while he is still asleep. Ether mixed with oxygen is administered through an intratracheal tube. During the progress of the operation the anesthetist must be ready at all times to aspirate secretions from the trachea. It is well also for the surgeon to work with the lung expanded as much as possible.

If the amount of secretion coming from the trachea should increase to the degree where it suggests the onset of excessive pulmonary congestion during the operation, tourniquets should be applied quickly by an assistant to all four extremities. It is wise to be prepared also for the performance of a venesection

in case of emergency, but this procedure has not been necessary in any of the six patients operated upon to date

Although it is necessary to have an infusion of dextrose solution running into a vein in case of emergency, the rate of flow must be slow. Blood is not used but should be available for use in case of hemorrhage

Technic With the patient lying on his left side, his right side arched slightly so as to widen the intercostal spaces, a standard thoracotomy incision is made. The pleural cavity is opened through the sixth intercostal space (or through the bed of the sixth rib if the rib resection technic is adopted). The wound edges are covered with pads of gauze moistened in sterile saline solution and a rib spreader is inserted. The lung is held forward by the hand of the first assistant and the pleura is reflected from the inferior pulmonary vein. The superior segment branch of this vein is identified and freed from the surrounding areolar tissue by sharp and blunt dissection. Any small tributaries which may be found must be ligated with fine silk and divided. The vein is followed upwards into the lung as far as its origin where two or three fairly large tributaries join beneath and slightly anterior to the lower portion of the superior segment bronchus. The vein is not divided until the freeing of the azygos vein has been accomplished (Fig 2)

The mediastinal pleura and retropleural fascia over the azygos vein are incised longitudinally. The azygos vein is freed from a point 2 or 3 centimeters below the level of the superior segmental vein upwards as far as its junction with the highest intercostal vein. In freeing the azygos vein it is usually necessary to ligate and divide a large number of its tributaries. These include the accessory hemiazygos, sometimes the hemiazygos, most of the right intercostal veins above the level of transection of the azygos vein, and many small esophageal and other mediastinal branches. Occasionally in order to gain sufficient length for the performance of the anastomosis, it may be necessary to divide the right highest intercostal vein. This was necessary in two of the six cases.

A short clamp, "bulldog" type, is applied to the superior segment vein as closely as possible to its junction with the basal segment branches of the inferior pulmonary vein. A hemostatic forceps is then applied as far into the lung as necessary to avoid sacrificing any of its length and the vein is cut close to the hemostat. A suture ligature of heavy silk is used to tie the pulmonary end of the vein. A bulldog clamp is placed across the azygos vein at the upper limit of the dissection and the vein is ligated and divided at the lower limit approximately 2 centimeters below the level of the pulmonary vein (Fig 3)

The blood is flushed out of each of the severed veins with saline solution, using a blunt needle attached to a small syringe. A Blakemore-Lord vitallium tube having a diameter of proper size to permit cuffing back the azygos vein on it is then applied to the upper or cardiac end of the azygos vein. The end of the azygos vein is passed through the tube and turned back to the ferrule

near the flange where it is tied with heavy silk. Three strands of arterial silk suture material are passed through the end of the pulmonary vein at equidistant points. Short hemostatic forceps are fastened to these strands about 2 inches from the end of the vein. A curved hemostat attached to the

FIG 2

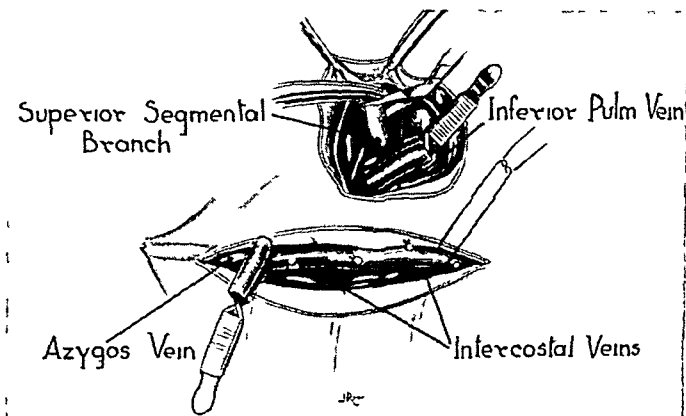
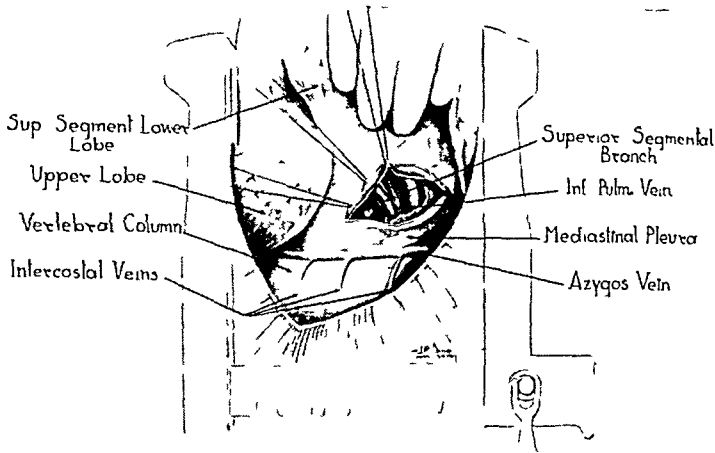


FIG 3

FIG 2—Drawing made at operation (Case 3) to show the superior segmental branch of the inferior pulmonary vein after completion of the dissection but before it has been severed. Azygos vein shown before dissection.

FIG 3—Drawing showing the completed dissection of both veins as they are about to be cut across. The bulldog clamps are in correct position. Ligature on the azygos vein ready to be tied preparatory to division approximately 2 cm beyond the level of the pulmonary vein. Hemostat in place on the superior segmental branch of the inferior pulmonary vein preparatory to division with fine straight scissors.

flange of the tube is used to hold the end of the azygos vein and direct it into the open end of the pulmonary vein which is drawn over it by exerting traction on the three strands of silk. The pulmonary vein is drawn up over the proximal ferrule on the tube where it is held with a silk tie. A second

ligature is then applied to hold the veins together close to the tip of the tube in the manner described by Blakemore and Lord⁵ (Fig 4)

The bulldog clamp is removed from the azygos vein first and then that from the pulmonary vein. In a moment the blood can be observed flowing briskly from the high pressure area in the pulmonary vein to the low pressure region in the azygos vein. Palpation of the latter beyond the anastomosis reveals the presence of a soft thrill.

A small incision is made in a lower intercostal space posteriorly and a large catheter is inserted for drainage. The lung is then expanded fully and the chest wall is closed.

The Blakemore-Lord non-suture method of anastomosis was chosen in preference to the suture method for two reasons. In the first place it avoids the presence of suture material in the intima of the veins and tends to minimize the danger of thrombosis. This danger may be more theoretical than actual, but it is not known how long a swift flow of blood will persist through the shunt, which is the only factor beyond the use of anticoagulants which can be depended upon to overcome a tendency to thrombosis. In the second place, the two veins which are used for the anastomosis are exceedingly fragile and small in diameter so that the suture method would be unusually difficult. Experience with the Blakemore-Lord tube method in the six cases reported seems to indicate that there is no reason to abandon its use.

OBSERVATIONS AT OPERATION

Appearance of the lung In all six patients operated upon thus far the

lung has shown a characteristic appearance. The color is dusky, not exactly cyanotic but rather suffused with a purplish red hue. It is unusually firm but becomes atelectatic quickly when the intrapulmonary pressure is released. This suggests that the firmness is due to the increased tension in the large pulmonary vascular bed rather than in the alveolar substance. There is always also marked dilatation of the bronchial and perihilar collateral veins. The pulmonary veins themselves are dilated, firm, and pulsatile.

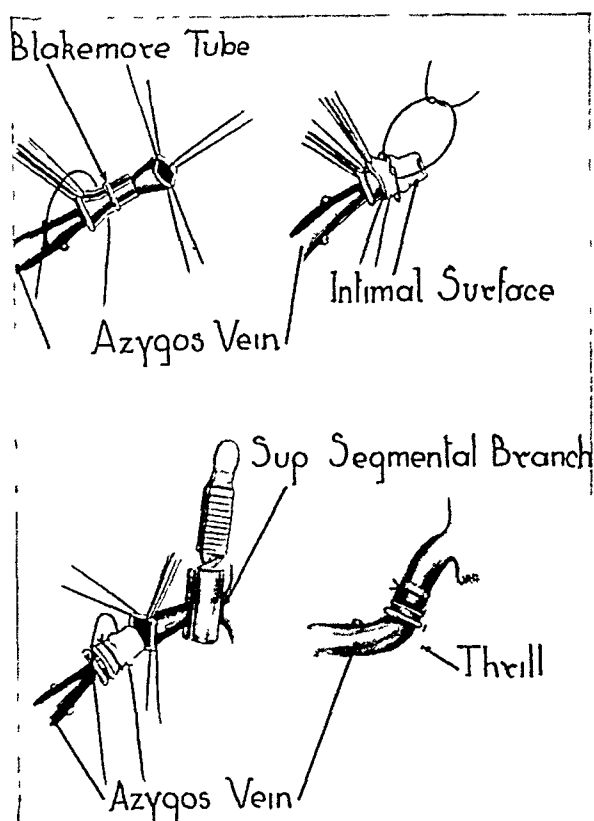


FIG 4—Drawing to show the several steps in the performance of the anastomosis by the Blakemore-Lord non-suture method as applied to the union of the azygos vein with the superior segmental branch of the inferior pulmonary vein. Completed anastomosis shown with location of thrill felt after the bulldog clamps have been removed.

Appearance of the heart The heart appears essentially normal except for the very tense dilated left auricle which can be seen bulging posteriorly and to the right into the field of operation

Appearance of the Superior Segment of the Lower Lobe after Ligation of Its Vein At the completion of the operation, the superior segment of the lower lobe has been observed in all cases to assume a dusky, dull red or purple color. In one patient (Case 5) who was on the verge of congestive failure during the course of the operation, this segment of the lung was actually hemorrhagic in appearance. These observations are consistent with the findings of Swan and Mulligan in experimental animals after ligation of the pulmonary veins⁶

EXPERIENCE WITH THE OPERATION—SIX CASE REPORTS

An anastomosis between the superior segment branch of the inferior pulmonary vein and the azygos vein has been performed in six patients with so-called "pure" mitral stenosis. Two of these were operated upon too recently for a satisfactory evaluation of the result. One died of an exacerbation of the rheumatic fever infection. The first three, however, have been enormously improved. None of these patients has ever experienced an attack of pulmonary edema since leaving the hospital. All three had been forced to adopt a life of semi-invalidism before the operation. Two of them were actually unable to carry on outside the hospital. All three are now leading normal lives after a prolonged period of disability before the operation was performed.

Complete details of the case histories are to be reported elsewhere.⁷ Brief abstracts are submitted here as follows:

Case 1—Mrs O C B (MGH 610979), 17-year-old mulatto girl, had rheumatic fever at age 5. Diagnosis of mitral stenosis was made at age 14. First attack of pulmonary edema occurred at age 15, and thereafter she experienced numerous attacks with cough, orthopnea, wheezing, and expectoration of blood-streaked sputum. The attacks occurred often during menstrual periods. One attack almost resulted in death. At this time she was in an oxygen tent for 4 days. Between attacks she experienced dyspnea, and was forced to give up school. She was admitted finally to hospital where she had several slight attacks even under treatment with digitalis, low sodium diet, and diuretics.

Examination revealed a slight cardiac enlargement, with a characteristic murmur of mitral stenosis. Electrocardiogram was normal, save for right axis deviation. There was no evidence of right side cardiac failure.

Operation March 23, 1948. The lung was characteristically dusky, not adherent. The superior segment vein was short (not over 1 cm). The azygos vein was slightly larger than the superior segment vein in diameter. A Blakemore-Lord tube non-suture anastomosis was performed. The flow of blood through the shunt was excellent. A thrill was felt.

Pressure in the left auricle before making the anastomosis was 460 mm of water. It was not thought wise to take the additional time at the end of the operation for a pressure reading after completion of the anastomosis.

Subsequent Course Her immediate recovery was rapid and uncomplicated. She was allowed out of bed on the third postoperative day. Since her discharge from the hospital she has led an unusually active life and has had no attacks of pulmonary edema. On

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one occasion, in August, 1948, she was admitted to the hospital with an attack of gonorrheal peritonitis with a fever of 103°F. It was discovered also that she was pregnant, and after a favorable response to penicillin therapy, she had an abortion (therapeutic) done. Her lungs remained dry throughout this illness. In January, 1949, she was admitted once again for interruption of a second pregnancy. No evidence of pulmonary edema was observed at this time.

Case 2—M Z (MGH 624098), 27-year-old male, entered July, 1948, because of recurring attacks of pulmonary edema. There was a diagnosis of rheumatic heart disease at age 17. First episode of pulmonary edema occurred in 1945 at age 24. The attacks became frequent and increasingly severe. They were precipitated by emotional disturbances, physical exertion, or infections. Several had been almost lethal. Auricular fibrillation developed in May, 1948.

Examination On entry there was moderate cardiac enlargement with absolutely irregular rhythm, rate 120, characteristic murmurs. Râles could be heard at both lung bases. Blood pressure 120/70. During a three months' residence in hospital before the operation he had attacks of pulmonary edema varying from mild episodes of nocturnal dyspnea and wheezing to attacks of such severity that it seemed unlikely that he would recover. For a long time his condition was considered to be too precarious to contemplate operation.

Operation October 24, 1948. The operation as described was performed. The lung was tense and dusky in color. No pressure readings were made because of his precarious condition.

Subsequent Course On the afternoon of the day of operation there was a transitory episode of pulmonary congestion. From that time on, however, he made a gradual but satisfactory recovery. He is now well and is touring the United States in anticipation of his return to his home in South America. He has had no attacks of pulmonary edema since the day of operation.

Case 3—Mrs R O (MGH 638226), age 24, was admitted October, 1948. The first knowledge of any abnormality came as a result of an acute attack of pulmonary edema occurring during the course of a pregnancy in 1946 (age 22). Two other severe attacks had occurred since, one as a result of exertion, the other during an attack of "bronchitis." The last episode was the most severe and required treatment in a hospital. A fourth attack occurred just before entry. She had had a chronic cough for many months.

Examination This revealed a small heart with characteristic auscultatory signs. Blood pressure 105/75. Electrocardiogram normal except for right axis deviation and prominent P waves. Cardiac catheterization with the patient at rest showed a pulmonary artery pressure of 46 mm Hg systolic over 25 mm Hg diastolic, pulse 95. After gentle exercise (one minute) it was 75/35, pulse 116. Developed pulmonary edema during the exercise test. (Normal 25 ± 10 to 5, with little change on exercise.)

Operation November 18, 1948. The lung was not as dusky and firm as in Cases 1 and 2, but was distinctly abnormal. A very satisfactory anastomosis was made between the superior segment vein and the azygos vein. Pressure readings from the left auricle were 425 mm of water before the anastomosis and 390 mm of water after its completion.

Subsequent Course Her recovery was uncomplicated. Her cough disappeared. Has had no attacks of pulmonary congestion even during a severe upper respiratory infection. Cardiac catheterization on February 19, 1949, revealed a pulmonary artery pressure of 50 mm Hg systolic and 20 mm Hg diastolic, pulse 78 at rest. The pressure after one minute of exercise was 65 mm Hg systolic and 25 diastolic, pulse 95.

Case 4—D G (MGH 649017), age 42, female. Admitted January 21, 1949. She had rheumatic fever at age 14. Her first symptom referable to the heart was exertional

dyspnea noticed during her second pregnancy at age 34. The first severe attack of pulmonary edema occurred after exertion at age 38. At that time she had dyspnea and blood-tinged frothy expectoration. Diagnosis of mitral stenosis made at that time. From that time she experienced rapid progression of difficulty with frequent episodes of pulmonary edema. During the past year she had been forced to give up almost all normal activities and had experienced frequent attacks of pulmonary edema. She was hospitalized three times because of the severity of attacks. There was a history of transient left hemiplegia two and one-half years before admission. During the past four years she had been taking digitoxin and quinidine with regularity because of the tendency of her heart to develop auricular fibrillation.

Examination The auscultatory signs were characteristic of mitral stenosis. No evidence of enlargement. Blood pressure 100/60, pulse 88, normal rhythm. Cardiac catheterization revealed a pulmonary artery pressure after a period of rest of 40 systolic and 10 diastolic with a pulse of 78. After exercise the pulmonary artery pressure rose to 104 systolic and 40 diastolic with a pulse rate of 100.

Operation (January 31, 1949) The lung was not as congested and cyanotic in color as in the other cases and there was much less evidence of increased collateral circulation round the hilum of the lung. The usual anastomosis was made and on release of the clamps the blood began promptly to rush through the anastomosis into the azygos vein and the function of the shunt was very satisfactory. Pressure readings were taken and it was noticed that after this procedure the flow of blood through the anastomosis was nowhere near as great as it had been before and it was quite obvious that it is unwise to occlude the vein even temporarily after the anastomosis has been made.

Subsequent Course Postoperative course quite satisfactory except for moderate pulmonary edema on second postoperative day. The patient was treated with oxygen, morphine, mercurhydrin. She developed a pulmonary embolus on sixteenth postoperative day. A bilateral superficial femoral vein ligation was performed in an effort to prevent further emboli. Convalescence was uneventful thereafter, and patient was discharged from hospital on February 26, 1949. Postoperative pulmonary artery pressure determinations will be made in the near future.

Case 5—A P (MGH 106907), age 30, female. She had no history of rheumatic fever, but a diagnosis of mitral stenosis was established at age 19. She first noticed dyspnea on exertion and orthopnea at age 25 during pregnancy. During the sixth month of her pregnancy she experienced a very severe attack of pulmonary edema, because of which the pregnancy was interrupted by cesarian section. Since then she had experienced rapid progression of difficulty, with frequent attacks of pulmonary edema, often several mild attacks per day. She had subacute bacterial endocarditis 16 months before admission which responded favorably to treatment with penicillin.

Examination There was no venous distention, but scattered inconstant fine inspiratory basal rales. Dullness and diminished breath sounds at right base posteriorly suggesting fluid. Her heart was markedly enlarged to the left, with a maximum palpable impulse in the midaxillary line, fifth interspace. There was a loud, grade III to IV mid-diastolic murmur over entire precordium and left back, loudest at apex. Venous pressure in the left forearm was 123 mm of water. Vital capacity was 1.8 liters (57 per cent of normal). Pulmonary artery pressure was 110/30 mm of mercury at rest, with pulse of 95, and 145/65 after exercise, pulse 125.

Operation (February 7, 1949) An effusion of slightly turbid pleural fluid was found and 325 cc was obtained on aspiration. The lung showed a very suffused, dull, purplish red appearance. There was a large development of collateral vessels throughout the hilum of the lung involving tissues between fissures and around bronchi and pulmonary vessels. The lung was unusually firm. The pleura was very much thickened and reddish in appearance, as though there had been inflammation present. Pressure within the auricle was 530 mm of water. Anastomosis was performed without difficulty. Pressure

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reading following anastomosis was 379 mm of water. The flow of blood through the shunt was unusually forceful. A marked thrill was felt in the azygos vein beyond the anastomosis.

Subsequent Course An attack of pulmonary edema immediately postoperatively was relieved by tourniquets and morphine. Fever rose to 105 and 106°. The postoperative course was extremely stormy, requiring oxygen, digitalis, aspirin, and frequent use of morphine and tourniquets for pulmonary edema. She gradually improved, but on the tenth day postoperatively developed tachycardia and pulmonary edema and died suddenly on the eleventh day. Autopsy revealed marked evidence of an exacerbation of rheumatic fever. There were fresh vegetations on the heart valves. The venous shunt was patent except for a recent (6 to 24 hour) thrombus in the pulmonary vein, probably a terminal occurrence.

Case 6—E. R. (MGH 657333), age 27, female, was admitted March 31, 1949. There was a history of febrile illness suggesting rheumatic fever during childhood. Four years previously, she experienced a first attack of pulmonary edema with dyspnea and expectoration of frothy blood-tinged sputum. Subsequently she suffered similar attacks, especially during the previous year, with four severe episodes and several minor ones. She had a therapeutic abortion two months prior to admission.

Examination Auscultatory signs were consistent with mitral stenosis, with only slight cardiac enlargement, lungs clear, pulse 76. Roentgen examination of the chest showed enlargement of left atrium. Vital capacity was 2.8 liters. Hemoglobin 14.4 Gm per cent. Pulmonary artery pressure while resting was 41 mm of mercury systolic and 18 diastolic, with pulse 75; after exercise 65 mm mercury systolic and 28 diastolic, with pulse 98.

Operation (April 11, 1949) The lung showed the characteristic congested appearance, no adhesions, left auricle very large, pressing the esophagus to the right. The azygos vein was unusually small in diameter but a satisfactory anastomosis was made using a 3 mm Blakemore-Lord tube. The flow of blood through the shunt was active. The pressure in the left auricle before the anastomosis was 460 mm of water, after the anastomosis it was 370 mm of water.

Subsequent Course The patient has made an uneventful convalescence to date, but is still in hospital. It is too early for evaluation.

COMMENT

The clinical improvement in the first three patients since the performance of the operation has been striking. Their exertional dyspnea and palpitation have diminished. None has experienced any attacks of pulmonary edema even under the stress of illness, emotional strain, and considerable degrees of physical exertion.

It has been demonstrated on the operating table that the shunt produces a significant lowering of the pressure in the left auricle. In one case there was a drop from 425 to 390 mm of water (or 8.2 per cent of the initial pressure). In another the drop was from 530 to 379 mm of water (or 28.4 per cent of the initial pressure). In a third the pressure fell from 460 to 370 mm of water, a drop of 19.5 per cent. Just how great a reduction in the intra-auricular pressure can be induced without impairment of the peripheral circulation is not yet known, but experience thus far has not suggested that any unfavorable result has been produced.

In one patient, (Case 3), completed catheter studies demonstrate a continuation of the decrease in pressure in the pulmonary circuit after the establishment of the anastomosis (Table I)

The preliminary experiences which make up the substance of the report suggest that at least until some more adequate method is available, the per-

TABLE I—*Pressure Determinations in Six Patients Operated Upon*

		Left Intra-Auricular Pressure During Operation (MM Water)		Pulmonary Artery Pressure (MM Mercury)			
		Before Anastomosis	After Anastomosis	Resting		After Exercise	
				Pressure	Pulse	Pressure	Pulse
Normal		100±		25± — 0-5		No change	
Case 1	460	N D		Before N D	N D	N D	N D
O C B				After N D	N D	N D	N D
Case 2	N D	N D		N D	N D	N D	N D
M Z							
Case 3	425	390		46		75	
				Before —	95	—	116
				25		35	
				After 50		65	
R O				—	78	—	95
				20		25	
Case 4	450	N D		40		104	
				Before —	78	—	100
				10		40	
				After N D	N D	N D	N D
Case 5	530	379		110		145	
				Before —	95	—	125
				30		65	
				After Died			
Case 6	460	370		41		65	
				Before —	75	—	98
				18		28	
				After N D	N D	N D	N D

N D — Examination not done

formance of an anastomosis between the pulmonary and the systemic venous systems may serve to overcome the effects of excessive pressure in the pulmonary circulation resulting from extreme degrees of stenosis of the mitral valve

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DISCUSSION—DR ALFRED BLALOCK, Baltimore Dr Sweet is certainly to be congratulated on his excellent results in these extremely ill patients As he has indicated, surgical attacks have been carried out, experimental and clinical, along several different lines One, a direct attack on the valve itself, second, a decompressing procedure, such as Dr Sweet has used, third, a by-passing type of procedure, in an attempt to cause blood to flow from the left auricle to the ventricle, circumventing the valve

(Slide) The attacks on the valve itself are demonstrated in this slide In 1922 Drs Graham and Allen, in this city, attempted to use a cardioscope with a concealed knife in visualizing and in cutting the stenotic mitral valve Dr Sweet has referred to the work of Cutler and Beck on the use of the valvulotome as shown in this slide More recently the late Dr Horace Smithy used this method with encouraging results

Dr Sweet also referred to the work of Harken and of Bailey, in which they make the attack on the commissure itself, rather than on the valve leaflet, attempting to avoid an insufficiency Harken uses a valvulotome He has operated on five patients, with two survivals Bailey uses a curved knife inserted alongside the finger, and attempts to cut the valve at the commissure He has operated on approximately a dozen patients, with four survivals

(Slide) Next is the method which Dr Sweet has used with great success, namely, a decompression procedure He spoke of the possible use of creating an inter-auricular defect, thereby converting the lesion into a Lutembacher's syndrome

(Slide) Dr Hanlon and I have devised what we consider a satisfactory method for creating an inter-auricular defect It can be done under direct vision It is dependent upon the fact that the right pulmonary veins are adherent to the posterior wall of the right auricle, and with proper occluding devices one may make an incision into the pulmonary vein, another incision into the auricle, and excise part of the septum

(Slide) The closure is relatively simple, in that one simply approximates the anterior wall of the auricle to the anterior wall of the vein

(Slide) Here is an example of such an interauricular defect We have not attempted to use this in patients with mitral stenosis thus far We have used it on approximately a dozen patients with transposition of the aorta and the pulmonary artery, and in one patient with a tricuspid atresia

(Slide) With the dexterity of Dr Sweet it is perfectly obvious that he can get by with an end-to-end anastomosis between the veins, but anastomoses between veins are particularly apt to thrombose, and I think an inter-auricular defect is somewhat more apt to stay open

The third and last general method of attack, which I think is still in the experimental stage, is that of a by-passing procedure, first suggested, I think, by Dr Jeger in Germany in 1913, in which he suggested that one attempt to by-pass the stenotic mitral valve by using a vein graft connecting either the auricle or the pulmonary vein with the left ventricle. I am afraid, however, that the valves in the vein would become incompetent.

More recently Rappaport has suggested the anastomosis of the left auricular appendage to the left ventricle. I am quite confident that this anastomosis will thrombose. I understand that Dr Robert Gross is now using (at least experimentally) a graft of aorta connecting the auricle and the ventricle.

From a theoretical point of view this method would seem to be the best of all. As to whether the technical features can be worked out, I don't know.

In closing, I would like to urge a vigorous continuation of attempts to produce mitral stenosis satisfactorily in animals. I think the reason this problem has been rather slow in progressing is this difficulty in producing it experimentally. Further more, again I would like to congratulate Dr Sweet on this excellent work.

DR HENRY SWAN, Denver, Colo. Gentlemen, I would like to thank you for this privilege of having the floor a moment to discuss this extremely stimulating paper by Dr Sweet.

We have been interested for some time in investigating both the technical methods and the physiological effects of creating a shunt between the pulmonary and the systemic venous systems. I would like to mention two observations which we have made in regard to this procedure.

(Slide) This slide shows various methods which we have studied in an attempt to make such a shunt. The type of anastomosis which most consistently resulted in a well functioning shunt is illustrated in "D." This is an end-to-end anastomosis between the azygos vein and the upper branch of the pulmonary vein, using a vitallium tube technic. When one does this, of course, one has to ligate the distal end of the vein.

This is followed in our experience by an intense engorgement of the pulmonary tissue, but over a period of about four months this gradually resorbs until the lung tissue returns approximately to normal. In other words, there is no death of the pulmonary tissue, as has been previously reported, and therefore this procedure would be safe if too great an obstruction to the venous return is not made.

(Slide) This slide shows a typical example of a specimen eight weeks after operation, with the probe which has a handle about 4 millimeters in diameter extending from the pulmonary vein to the vena cava.

The second observation is in regard to the physiological effects of such a procedure. As Dr Sweet pointed out, the purpose underlying the operation is a reduction in the pressure of the pulmonary system by making the shunt from the high pressure area, that is, the pulmonary veins, to a low pressure area—the vena cava. One hopes thereby to prevent or delay the right-sided heart failure.

It must be admitted, however, that in so doing one substitutes a marked increase in the blood flow through the right side for the decrease in pressure.

(Slide) This slide illustrates diagrammatically the situation as it relates to the hemodynamics following such an operation. You will observe that the artificial shunt in this area results in a certain amount of blood, illustrated here as the stippled area, which must continuously pass through the right side of the heart. This can be accomplished only by diminution in the output on the left side of the heart.

Whether in the long run it is better for the right ventricle to have an excessive output against a somewhat diminished pressure, in contrast to a smaller output against a high pressure, only time will be able to tell.

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One final point is in regard to the selection of patients for clinical trial. We are all familiar with the fact that in almost all conditions in which there is a pulmonary hypertension, organic changes occur in the peripheral pulmonary arterioles, quite similar to those which are seen in the systemic arterioles in generalized hypertension.

Such changes are commonly seen in patients with mitral stenosis. If they are present it would seem probable that such a shunt might not result in a lowering of pressure in the pulmonary artery, but indeed might have the opposite effect by increasing the right heart output into a pulmonary bed which is contracted by organic arterial disease.

I would like to ask Dr. Sweet if biopsies were taken on the lungs of any of his patients upon whom he has operated, as this might shed considerable knowledge on this particular point. I should think that if this particular operation were to have its best chance, it would be done early in the course of the disease, before right-sided heart strain has occurred and before there has been any pulmonary arteriolar change.

DR. FREDERICK E. KREDEL, Charleston, S. C. I should like to say just a word about the problem of insufficiency after valvulotomy.

A little over a year ago Dr. Smithy operated on a series of seven cases of mitral stenosis, with five survivors. In two of these cases the valve was apparently missed, so we cannot count those. One other case subsequently died and did have a little insufficiency, but this was apparently not related to the valvulotomy itself.

In the two other cases, now about one year postoperative, the stenosis has been relieved clinically, and there has been no trouble from mitral insufficiency.

DR. RICHARD H. SWEET, Boston. All of us should be most grateful to Dr. Blalock for his excellent historical review, and to Dr. Swan for his valuable review of the physiologic mechanisms involved in this procedure. I would like also to reiterate the necessity for recreating this condition in animals, and along that line to state that until I had operated on my first patient I was unaware of Dr. Swan's valuable contributions in the experimental animal.

We have not attempted to do this in animals because we, likewise, have failed to create mitral stenosis in any of the experimental animals, and I felt that unless one could reproduce the disease which we are operating upon, there was hardly any wisdom in trying to attempt it on them.

With regard to the choice of patients, of course it is quite obvious that this should not be applied to all cases of mitral stenosis, and I am certain that in fact as we review the cases it will be applicable only to a certain few. Those will be the ones that have hearts that are not enlarged, who have not begun to suffer from the prolonged effects of the disease.

We have done biopsies on the lung. I am not certain about whether I could give any useful information at this point without reviewing the slides regarding the vessels. We were particularly interested in determining, if possible, what it was which made the peculiar appearance in the roentgen-ray films in these patients after recovery from a series of episodes of mitral stenosis. In other words, the lungs of some of these patients looked almost as if they had had miliary tuberculosis, or a certain amount of persistent pulmonary congestion. In fact, that appearance is due to the deposits of hemosiderin which one sees. We will review our slides to see what the vessels look like.

I would like also to point out that this naturally is nothing but a preliminary presentation, and it is a procedure which may ultimately not be of any value, but I am absolutely certain, on the basis of clinical observation, that at least four of these patients are for the moment completely rehabilitated.

THE VALSALVA MANEUVER, AN AID FOR THE CONTRAST VISUALIZATION OF THE AORTA AND GREAT VESSELS*

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RADIOGRAPHIC VISUALIZATION of the vascular system requires a high local concentration of radiopaque dye. In large vessels where the volume flow of blood is great, a sufficient concentration of dye can be achieved by temporary obstruction of the artery proximal to the site of injection. Although this procedure can be carried out with relative ease in the peripheral arteries, it is difficult if not impossible to accomplish this result in the more centrally placed vessels. In retrograde arteriography,^{1, 2} it is particularly difficult to obtain a sufficient concentration of dye, since, as Farinas³ has shown in the experimental animal, the injection, to be successful, must overcome first the inertia of the blood flow and, second, the blood pressure. In a previous study,¹ repeated attempts to visualize the abdominal aorta by retrograde injection of dye into the femoral artery were unsuccessful, in spite of the use of a large needle, 15 or 16 gauge, and the injection of 30 to 40 cc of 35 or 70 per cent Diodrast. Since proximal compression of the abdominal aorta, especially in its upper portions, was impossible, it was felt that better visualization might be accomplished if some method could be devised for temporary suppression of cardiac output, so that neither the blood pressure nor the volume flow of blood would interfere with the injection of the radiopaque solution.

The Valsalva maneuver was selected as a means for temporary reduction of the cardiac output at the time of the injection of the radiopaque material into the arterial system. The results obtained in a series of 13 cases form the basis for the present communication.

TECHNIC

The following technic has been gradually evolved in the course of these observations, and has been found to be satisfactory in the majority of cases.

The patient is placed supine on a horizontal cassette tunnel, the long axis of the tunnel and the long axis of the roentgen ray table on which it is placed run in the same direction. The tunnel, open at both sides and accommodating a 14 by 17 cassette lengthwise of the table, is put into position in a rack.

This rack has grooves which accept two large lead screens extending from the tunnel in wing-like projections on either side. This is for the protection of

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the films and the operator. On the side of the table away from the operator is a bin, lined with sponge rubber, into which the cassettes fall as they are pushed through the tunnel. The tunnel has a bakelite cover, beneath which are grooves to accept a 14 by 17 Lysholm grid. The channels in the tunnel through which the 14 by 17 cassettes travel have springs at the far end to arrest this travel.

The apparatus is fed by hand, and the exposures are made with a foot switch. Six or seven films are used, and all of the exposures can be made in eight to ten seconds, depending upon the speed of the operator. The interval between the first and second films is usually the closest, due to the fact that one cassette is already in place. The technical factors vary with the vessel to be visualized.

Abdominal Aorta (1) (Outlined by retrograde carotid injection, using the Valsalva maneuver) 86 to 92 KV, 0.2 sec, 200 MA, 36-inch tube film distance. Exposures are made as rapidly as possible beginning just before completion of the injection. (2) (Retrograde injection of the femoral to outline the abdominal aorta and common iliac using the Valsalva maneuver) Exposures are started at the beginning of injection and are made as rapidly as possible, using the same factors as noted above.

Femoral Artery 85 KV, 0.15 sec, 200 MA, 36-inch tube film distance. Exposures are made as rapidly as possible, starting when injection is half completed.

Popliteal and Tibial Vessels 75 KV, 0.1 sec, 200 MA, 36-inch tube film distance. Injection is made in the femoral artery. Exposures are made starting with completion of injection. The first two films are exposed one second apart and the later studies made at gradually increasing intervals. Total time for six films is approximately 15 seconds.

Foot and Ankle 68 KV, 0.05 sec, 200 MA, 36-inch tube film distance. Injection is made into the femoral artery. Exposures are started at completion of injection. The first two are made within five seconds, and the remainder every five to eight seconds for a total of 30 to 45 seconds.

Thoracic Aorta (Outlined by retrograde carotid injection using the Valsalva maneuver) 86 KV, 0.2 sec, 200 MA, 36-inch tube film distance. Exposures are started at the beginning of injection and made as rapidly as possible.

Forearm and Hand The method is similar to that in the leg and foot. 60 KV, 0.05 sec, 200 MA, 36-inch tube film distance. Exposures are started when two-thirds of the injection has been made and they are spaced about every three seconds for a total of 15 to 18 seconds.

The selection of the radiopaque substance is determined by the portion of the vascular system selected for visualization. Thorotrast in a concentration of 20 per cent is non-irritating, and is therefore generally used in the presence of severe obliterative arterial disease or when there is any chance that the contrast medium may enter the intra-cranial blood vessels. Thorium dioxide is not rapidly excreted, and since there may be some damage from persistent

TABLE I

Case No	Sex	Age	Date	Clinical Diagnosis	Artery Injected	Size Needle	Contrast Medium	Complications	Comments
1	M	57	6/4/48	Aneurysm abdominal aorta	Rt superficial femoral	16	40 cc 70% Diodrast	0	Unsatisfactory Failure to visualize aneurysm
2	M	45	7/7/48	Aneurysm thoracic aorta	Lt common carotid	16	2 injections 50 cc 70%	Convulsions, temporary rt hemiplegia	Satisfactory with Valsalva maneuver
3	M	67	1/28/49 2/3/49	Bilateral femoral aneurysms	Lt carotid Rt femoral	18 16	30 cc 70% Diodrast 50 cc 35% Diodrast	0 0	Satisfactory Multiple aneurysms of femoral and iliac arteries
4	M	48	2/4/49	Thrombosis rt common iliac artery	Lt common femoral	16	50 cc 70% Diodrast	0	Satisfactory Rt femoral filled through collaterals
5	M	60	2/4/49 2/7/49	Aneurysms bilateral popliteal and abdominal	Rt femoral Lt common carotid	16 16	50 cc 35% Diodrast 2 injections 50 cc Thoro trast each	0 Dissecting aneurysm aorta Myocardial infarction	Unsuccessful Unsuccessful
6	M	69	2/11/49	Bilateral common femoral thromboses	Lt common carotid	18	40 cc Thoro trast	0	Satisfactory Obstruction on left confirmed at operation
7	M	50	2/21/49	Thrombosis	Rt common carotid	18	33 cc 70% Diodrast	Brain stem damage	Satisfactory Thrombosis of subclavian axillary and brachial arteries demonstrated

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TABLE I—Continued

Clinical No	Sex	Age	Date	Clinical Diagnosis	Artery Injected	Size Needle	Contrast Medium	Complications	Comments
8	M	49	2/24/49	Aortic thrombosis	Lt common carotid	16	45 cc 70% Diodrast	0	
9	I	49	3/3/49	Lt subclavian aneurysm	Lt brachial	18	25 cc 35% Diodrast	0	Poor aortic filling but filling of femorals through collaterals
10	F	67	3/5/49	Polycythemia	Lt common femoral	18	20 cc Thorotrast	0	Satisfactory Arteriosclerotic plaque in subclavian artery, vertebral visualized
11	M	32	3/18/49	Rt femoral A-V	Rt femoral	18	30 cc 35% Diodrast	0	Satisfactory Multiple occlusions of digital vessels
12	M	63	3/29/49	Rt common iliac thrombosis	Lt common femoral	15	50 cc 35% Diodrast	0	Unsuccessful Failure to show fistula even with Valsalva maneuver
13	M	25	4/1/49	Post operative repair of fistula of rt popliteal and post tib arteries	Rt posterior tibial	18 Lindemann needle	20 cc 35% Diodrast	0	Satisfactory with Valsalva maneuver
									Satisfactory, normal arteries

radio-activity,⁵ its use has been reserved for those patients with degenerative arterial disease whose life expectancy is not great. Thirty-five per cent Diodrast has been found to give less reaction than the 70 per cent Diodrast, and it has been selected for the visualization of the smaller arteries. In those arteries with a large volume flow, for example in retrograde arteriography of the aorta by way of the common carotid arteries, 70 per cent Diodrast has given more satisfactory visualization.

The complications which have resulted from the injection of radiopaque substance during the Valsalva maneuver will be discussed in detail in the consideration of the individual cases.

After the preliminary film has been seen by the radiologist and the surgeon, and any necessary corrections in technic made, the needle is inserted into the artery through the skin or after exposure of the artery under local anesthesia. A number 15, 16 or 18 gauge needle has been used for the femoral and carotid arteries, and for the smaller arteries a No. 18 Lindemann cannula has been found quite satisfactory. This needle is attached to a stop-cock by way of a segment of rubber tubing eight inches long. The rubber tubing is fitted with a "Luer-lok" attachment so that it cannot be detached from the needle. A 50 cc syringe containing the contrast medium, with a "Luer-lok" connection, is fitted to the stop-cock on the proximal end of the rubber tubing. The use of this section of rubber tubing has been found to be essential in order to prevent dislodgement of the needle from the artery during the forceful injection. While the operator holds the needle in the lumen of the vessel, the assistant grasps the barrel of the syringe in one hand and the plunger in the other hand, in preparation for the injection. The patient is then instructed to take a deep breath, to close the glottis, and to strain down with all his might. If the artery has been exposed, the decline in blood pressure is readily perceptible to the index finger of the surgeon who is holding the needle in the arterial lumen. When the injection is being made directly through the skin, the disappearance of the pulse at the wrist or at the temple during the forced expiration against resistance serves as a guide for the injection of the contrast material.

When the blood pressure has fallen to a low level, the signal is given and the radiopaque solution is injected as rapidly as possible. Although the exact time of the injection has not been measured, it has been estimated that from two to five seconds is required for the injection of 30 to 50 cc of solution. The first film is exposed when about half of the contrast material has been injected, and thereafter the succeeding films are exposed every two to five seconds, depending upon the portion of the arterial system which has been selected for visualization. In the aorta and its major branches the cassettes are changed as rapidly as possible, every one to two seconds, while in the most peripheral arteries in the distal parts of the extremities longer intervals have been found more satisfactory. In patients with a high degree of arterial tone, it may be advisable to precede the visualization by injection of Procaine into the region of the sympathetic ganglia.

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It is advisable to have the patient practice the Valsalva maneuver several times before the injection in order to familiarize himself with the details. Again, the patient should be warned that he will experience a sensation of intense heat at the time of the injection, and that this painful sensation is of a temporary nature, but that he should refrain from any movement while the exposures are being made. If Diodrast is being used, preliminary tests for sensitivity, of course, are necessary.

RESULTS

The effect of forceful expiration against the closed glottis, the Valsalva maneuver, upon the blood pressure, is illustrated in Figure 2. There is a rapid

FIG 1

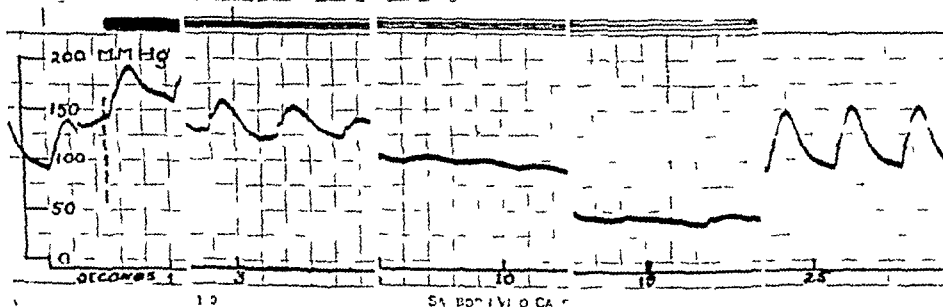
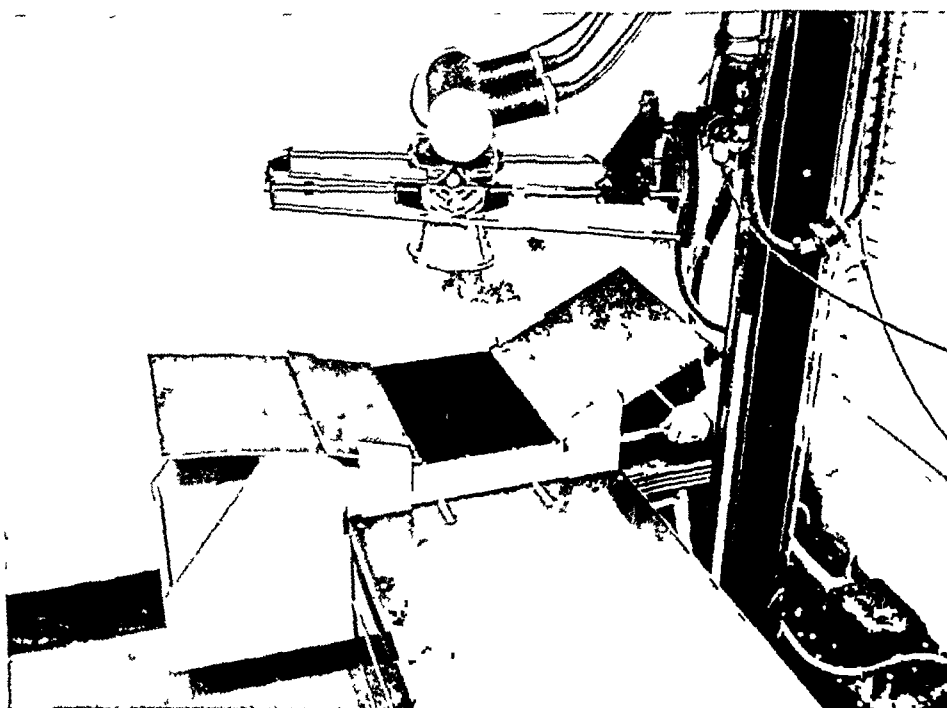


FIG 2

FIG 1—Rapid film changer. Exposure made by foot switch, films fall into bin as completed.

FIG 2—Arterial pressure tracing. Strain gauge recording of femoral blood pressure variations during a Valsalva maneuver. Dotted line shows point of commencement of expiration effort following maximal inhalation. Note drop in total pressure and pulse wave during 20-second interval of expiratory effort against a closed glottis. The last frame indicates the temporary overshoot of pressure following release.

decline in the blood pressure and pulse amplitude over a period of 20 seconds, in this particular subject the blood pressure as recorded by a strain gauge fell to 48 mm of mercury. Following release of the glottis the blood pressure rapidly rises and usually exceeds the initial level.⁴

The first retrograde arteriogram with the use of the Valsalva maneuver was performed in the following patient

Case 1—This patient, a man of 57, was admitted to the Franklin Hospital in June of 1948, with the chief complaint of intermittent attacks of abdominal pain of a year's duration. One year before admission he had been struck by a heavy case in the mid abdomen, and subsequently had experienced attacks of abdominal pain radiating into both flanks. His physician had noted a pulsating abdominal mass and roentgenogram of the abdomen had revealed a circular calcified shadow lying at the level of the fourth vertebral

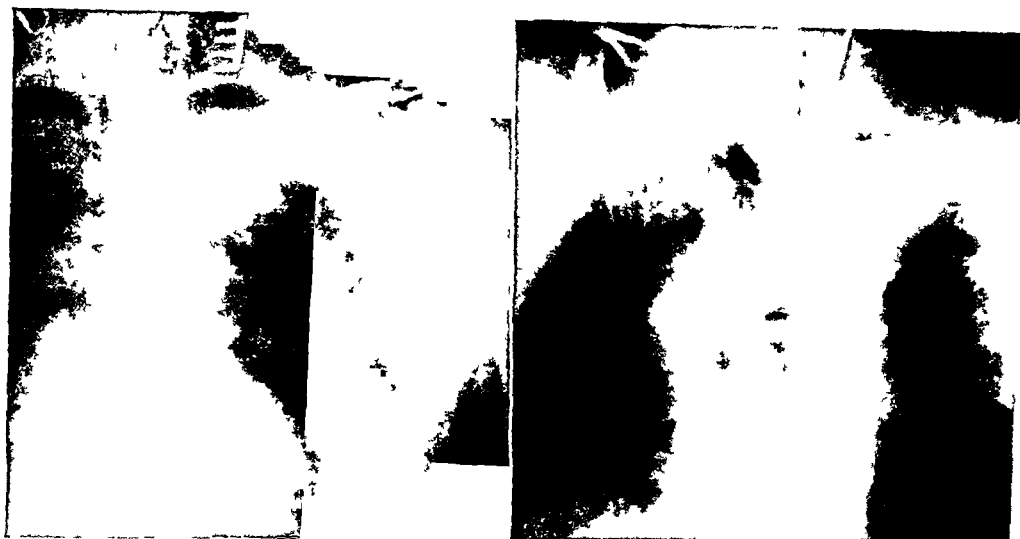


FIG 3 (Case 2)—Retrograde left common carotid arteriogram (A) Aneurysm of arch of aorta is faintly visualized (B) Clearer delineation of the same lesion with Valsalva maneuver and visualization of the ascending aorta

which had been interpreted as an aneurysm of the abdominal aorta. Retrograde arteriography of the abdominal aorta was performed by the injection of 41 ccs of 70 per cent Diodrast through a 16-gauge needle. With a special apparatus, the injection was made at a pressure of 100 lbs per square inch over a period of 3 seconds, and 2 films were exposed. The radiopaque material rose as high as the second lumbar vertebra, and by-passed the calcification seen on the left side of the vertebral column. As a result of this study, it was concluded that the calcified mass did not appear to be an aneurysm since it lay outside of the aorta.

Exploration through a retroperitoneal exposure was performed on June 11. The mass proved to be an aneurysm of the abdominal aorta which had apparently expanded on numerous occasions with resulting marked inflammatory scar tissue. After preliminary occlusion of the aorta above and below the aneurysm, the mass was opened but surgical repair was found to be impossible because of marked sclerotic changes in the wall of the aorta, where a defect measuring one inch in length and involving one third of the anterior wall was found. The aorta was completely divided above the sac and the opening closed with a running suture of No. 40 cotton. After operation in spite of the use of anticoagulant and supportive measures, there was marked retraction of the lower half of the body leading to the patient's death on the second postoperative day.

Comment Postmortem examination showed extensive degenerative arterial disease involving the aorta and iliac vessels. This was the first patient in whom the Valsalva maneuver was used for retrograde arteriography of the abdominal aorta, and although the roentgen ray films were better than any previously obtained, they still were not sufficiently clear to demonstrate the extensive arterial disease present and the communication of the aorta with the aneurysmal sac.

Case 2—This patient was a 45-year-old man, who was admitted to the Franklin Hospital in July of 1948 for an attempt at visualization of an aneurysm involving the transverse aortic arch. The patient had suffered massive hemoptysis in January, 1948, and at that time the diagnosis of a luetic aneurysm of the aorta was made. Retrograde arteriography using the left common carotid artery was performed on July 7, 1948. Under local anesthesia the left common carotid artery was exposed, and through a 16-gauge needle 50 cc of 70 per cent Diodrast were injected, with the patient in the dorsal recumbent position. The patient experienced some discomfort and nausea. He was then rotated into the left anterior oblique position, and the injection repeated, but this time using the Valsalva maneuver. The Diodrast was injected when the pressure in the carotid artery had dropped to a low level. In Fig 3 is shown a comparison of the intensity of visualization of the aorta and its large branches, with and without the Valsalva maneuver.

Twenty seconds after the injection of the Diodrast, the patient had a generalized convulsion which lasted for 30 seconds and was followed by a prolonged period of apnea with a slow and irregular pulse. When spontaneous respiration was finally resumed the patient was given nasal oxygen. After completion of the procedure, it was found that the patient had a right hemiplegia. He remained comatose for one-half hour and the convulsions recurred on three occasions. He was treated with nicotinic acid, 100 mg every four hours, and nasal oxygen, after a severe convulsion when the heart appeared to have stopped, he was given intracardiac adrenalin. Recovery finally took place without residual neurological symptoms, but the hemoptysis has recurred.

Comment The convulsions and temporary right hemiplegia in this case were probably due to an error in technic which allowed the 70 per cent Diodrast to reach the intracranial circulation in a concentrated form. As emphasized previously,² it is extremely important to aspirate the 70 per cent Diodrast from the left carotid artery after completion of the injection, and it is possible this was not done in this patient. Again, it is possible that the 70 per cent Diodrast might have entered the intracranial circulation by the right carotid and by both vertebrals (as shown in Figure 3B). In retrospect it would have been better to have used Thorotrast for this visualization.

Case 3—This patient was a 57-year-old man who was admitted to the Franklin Hospital in January of 1949 because of a pulsating mass in his right groin. His blood pressure was 230/150. On physical examination a pulsating mass was found in both inguinal regions. There was evidence of mild cardiac decompensation.

Retrograde carotid arteriography, using 30 cc of 70 per cent Diodrast through an 18-gauge needle, was attempted, but because of the patient's poor general condition, the Valsalva maneuver was carried out with caution and only mildly and the dye was not injected with as great force as usual. In serial films of the abdomen no dye was visible in the abdominal aorta below the level of the renal artery. The patient recovered from this procedure without complications.

On February 3, a retrograde arteriogram of the right femoral artery was obtained by insertion of a 16-gauge needle directly through the skin into the femoral artery just below the aneurysm in the inguinal region. The circulation below the point of insertion of the needle was temporarily obstructed by inflation of a tourniquet applied to the thigh, and 50 cc of 35 per cent Diodrast were injected. As shown in Fig 4 multiple saccular aneurysms of the right iliac artery were disclosed as well as a large fusiform aneurysm of the right external iliac and femoral arteries.

In view of the patient's generalized cardiovascular disease, operative treatment did not appear to be indicated.

Case 4—This patient was a 48-year-old man who was admitted to the Franklin Hospital in February of 1949 because of intermittent claudication involving the right thigh and leg of six months' duration. Although the left femoral pulse was readily palpable, no pulse could be felt in the right groin. The pulsation of the abdominal aorta appeared to be normal.

Under local anesthesia the left femoral artery was exposed in the groin, and 50 cc of 70 per cent Diodrast were injected through a 16-gauge needle over a period of four seconds while the circulation to the left-lower extremity was occluded by inflating a tourniquet placed about the thigh. Serial films were taken which showed obliteration of the iliac artery on the right side, with filling of the right femoral by means of collaterals across the pelvis from the left side.

Comment This patient was allowed to exhale before completion of the injection, so that filling of the abdominal aorta was not obtained. Even though the radial pulse disappears more completely immediately following release of the breath, it is apparently advisable to maintain the increased intrathoracic pressure during the entire period in which films are being taken.

Case 5—This patient was a 60-year-old man who was admitted to the University of California Hospital in January of 1949 because of a pulsating mass behind the left knee. In July of 1948 he had suddenly noted pain and numbness with

pallor and coldness of the left lower leg, but recovery had taken place. At the time of admission, he had a blood pressure of 210/130, his heart was enlarged and a pulsating mass was palpable in the lower abdomen. In addition there was dilatation of the left femoral artery. Retrograde arteriography by way of the right femoral was attempted on February 4, but was unsatisfactory due to the fact that the patient moved during the exposure of films. The patient's movement was probably due to the intense burning sensation from the injection of 35 per cent Diodrast.

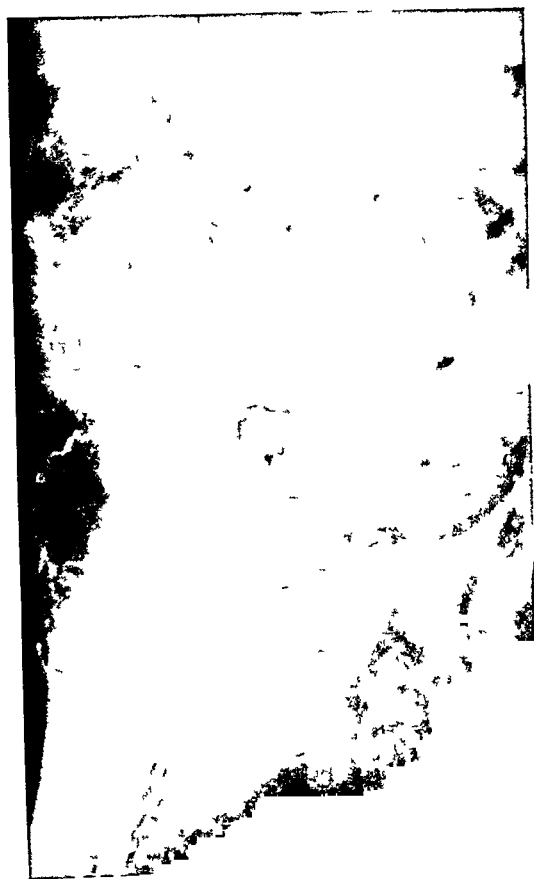


FIG 4 (Case 3)—Retrograde right femoral arteriogram. Aneurysms of femoral and iliac arteries are demonstrated.

THE VALSALVA MANEUVER

Retrograde carotid arteriography with the Valsalva maneuver was attempted on February 7, using Thorotrast. Two injections of 50 cc each of 20 per cent Thorotrast by way of the left common carotid artery were made. In spite of the use of the Valsalva maneuver, no dye appeared in the lower abdominal aorta or pelvis. It was the opinion of Dr. Earl R. Miller, of the Department of Radiology at the University of California Hospital, that some additional vascular lesion must have been present in the thorax to prevent the passage of radiopaque material into the abdomen.

At the time of the second injection of Thorotrast, the patient experienced a sensation of pressure in the thorax, but no significant pain. That night, some eight hours later, he had sudden onset of severe precordial distress, with a fall in blood pressure, and other

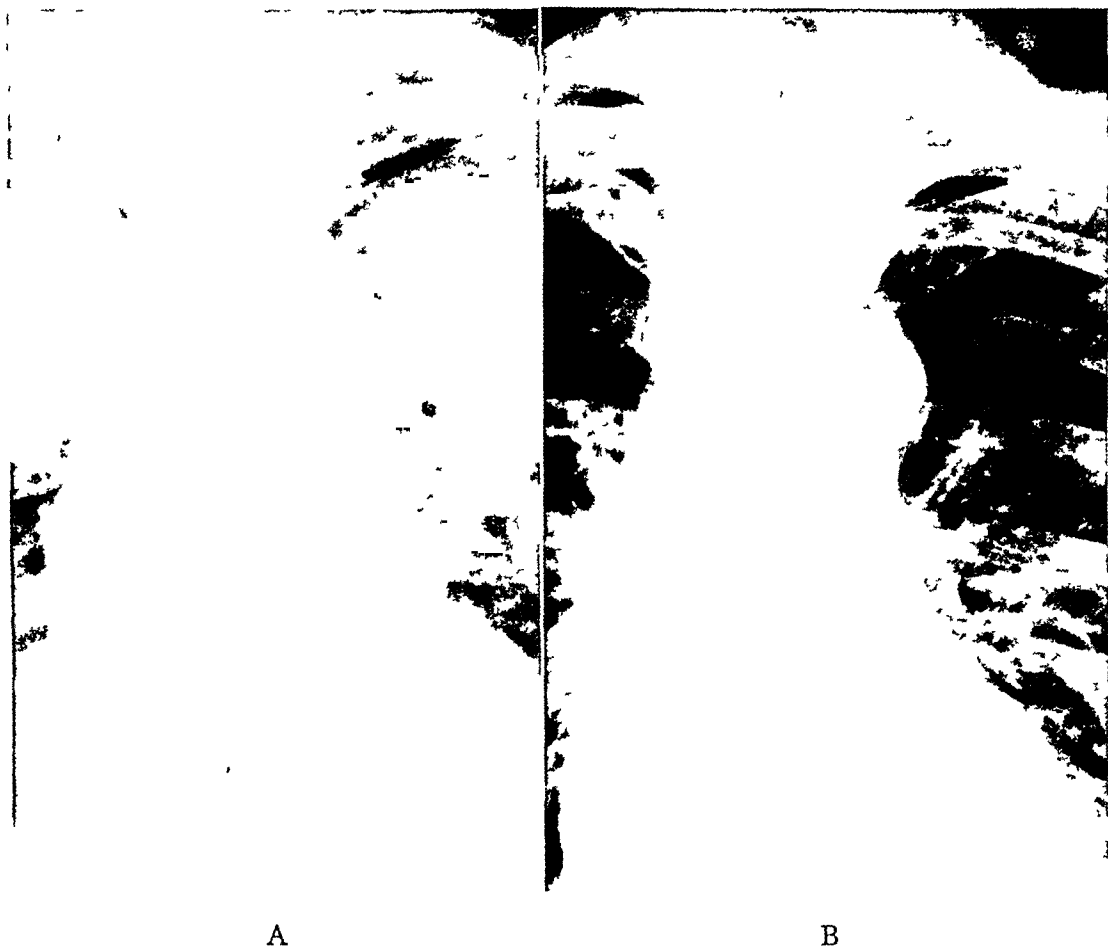


FIG 5 (Case 5)—Roentgenogram of chest (A) Preoperative film (B) Film ten days after retrograde carotid arteriogram, showing residual Thorotrast in wall of aorta

classical signs of acute myocardial infarction. The electrocardiogram showed typical changes, and there was an elevated sedimentation rate and fever with persistent chest pain for a period of 10 days. At the end of that time, however, a roentgenogram of the chest showed radiopaque material present within the wall of a dilated aorta as shown in Fig 5. Recovery finally took place.

Comment This patient probably had an unsuspected dissecting aneurysm of the thoracic aorta. During the period of hypotension from the Valsalva maneuver he might have sustained a coronary occlusion or else, possibly during the period of hypertension following release of the glottis, a further rupture of a dissecting aneurysm took place.

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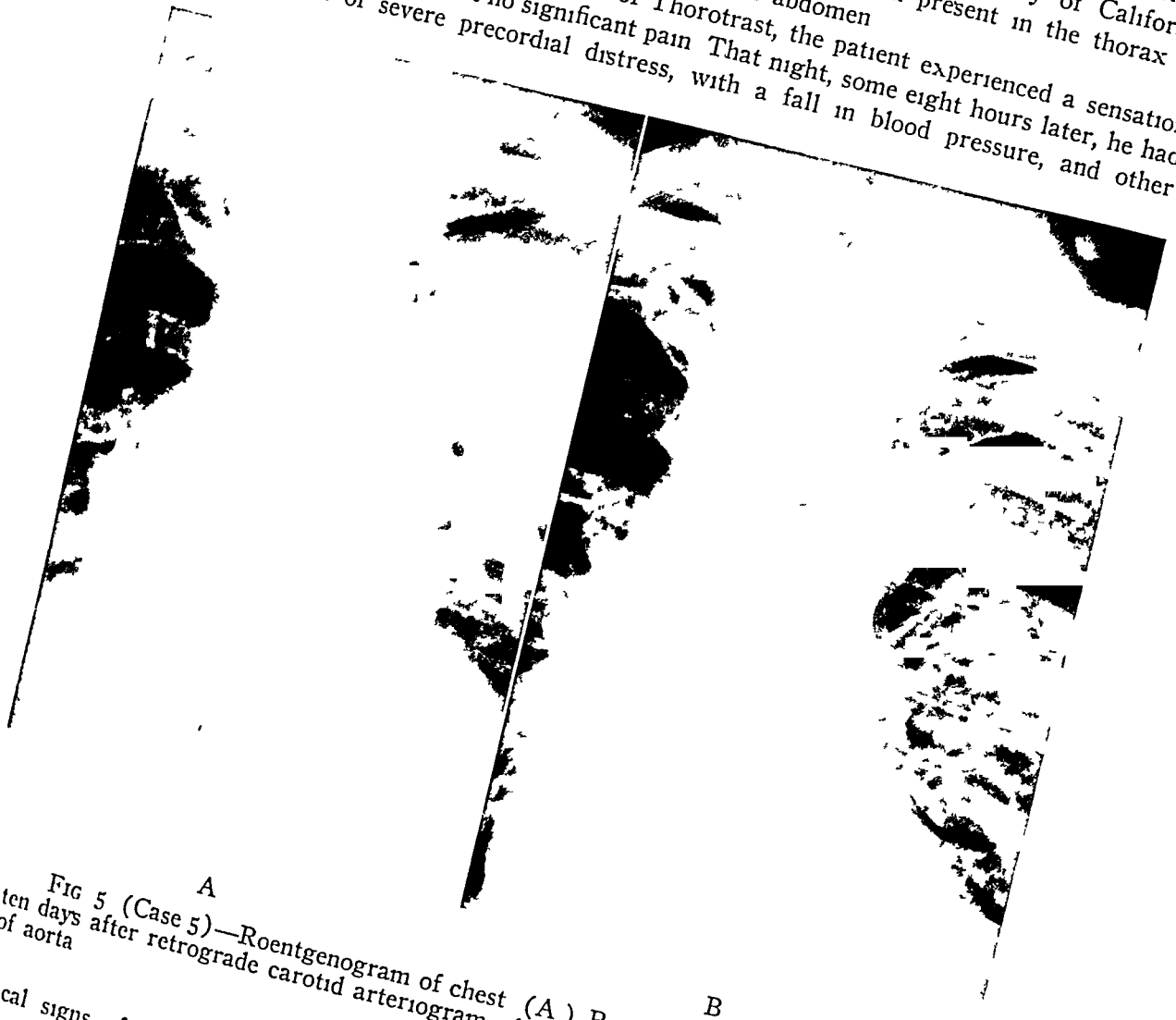


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Case 6—This patient, a 69-year-old man, was admitted to Franklin Hospital in February of 1949 because of a dull aching pain in both feet and lower legs which had been present over a year. On admission he complained of a constant pain in the region of his left ankle and in the metatarsal area. The left common carotid artery was exposed and 40 cc of Thorotrast were injected in a retrograde fashion through an 18-gauge needle at the height of a Valsalva maneuver. The entire injection required about 4 seconds. Serial roentgen-rays were taken immediately following the completion of the injection. These films demonstrated occlusion of the common femoral arteries bilaterally, which was confirmed on the left by operation. The occlusion on the left was probably acute with ischemic neuritis, while that on the right was of a more chronic nature. Temporary relief was obtained by left femoral arterectomy. Following recurrence of pain

FIG 6



FIG 6 (Case 7)—Retrograde carotid arteriogram with Valsalva maneuver. Serial films show obliterated subclavian, axillary and brachial arteries.

FIG 7 (Case 9)—Retrograde left brachial arteriogram. (A) Arteriogram without use of Valsalva maneuver demonstrating filling to the junction of the axillary and brachial arteries. (B) Same procedure with Valsalva maneuver demonstrating filling of the subclavian to its origin as well as of the vertebral. Note the narrowing of the subclavian artery at the origin of the vertebral.

relief was obtained by left lumbar sympathectomy after left lumbar sympathetic block had proved effective

Comment The retrograde arteriogram was useful in showing where the obstruction lay, so that a successful arterectomy could be carried out

Case 7—This patient, a man of 50, was admitted to the Franklin Hospital in February of 1949 because of burning pain, numbness, and paralysis of the right arm and hand of four months' duration. This state followed excision of a small tumor from the right axilla. The skin of the hand was glossy and cool, the joints were fusiform and fixed. Pulses were absent in the right wrist, however, the brachial was palpable at the elbow. The problem here was one of locating the point of arterial obstruction, of determining its extent, and its relation to the causalgic state.

Under local anesthesia the right common carotid artery was exposed and 35 cc of 70 per cent Diodrast were injected in a retrograde fashion at the height of a Valsalva maneuver. Films were exposed serially, the first being taken when half of the radiopaque material had been injected. This demonstrated obliteration of the subclavian, axillary and brachial arteries from the second portion of the subclavian to beyond the profunda brachii. The rapid injection of Diodrast combined with arterial obstruction and the Valsalva maneuver caused the medium to fill the internal mammary and vertebral arteries in high concentration. A posterior inferior cerebellar syndrome resulted from the concentrated Diodrast in the vertebral artery, from which recovery was gradual over a period of 3 weeks.

Comment Excellent visualization was obtained facilitating arterectomy in combination with sympathectomy and brachial plexus neurolysis to relieve this patient's painful syndrome. The use of 35 per cent Diodrast and concomitant occlusion of the vertebral artery probably would have avoided the brain stem injury.

Case 8—This patient was a 49-year-old man who was admitted to Franklin Hospital in February of 1949 because of a 3-year history of claudication in both hips. There was definite evidence of an arterial insufficiency in both lower extremities. The femoral pulses were palpable but that on the right was diminished. There were no palpable arterial pulsations distal to the femoral region. The left common carotid artery was exposed, a 16-gauge needle was introduced in a retrograde fashion, and 45 cc of 70 per cent Diodrast were injected into the left common carotid artery. The injection was carried out during a Valsalva maneuver, and roentgen-ray films were taken serially. The aorta and iliac arteries were shown to be very faintly outlined, the dye was seen entering the femoral artery, and the femoral profunda was well outlined.

Comment These films show poor aortic filling but good filling of the femorals by collaterals. The poor visualization was due to a combination of an inadequate Valsalva maneuver (limited because of the patient's condition), slow injection, and insufficient Diodrast.

Case 9—This patient was a 49-year-old woman physician, admitted to the Franklin Hospital in March of 1940 because of one year's history of numbness and paresthesia of the third, fourth and fifth fingers of the right hand. On examination all pulses were present both in the upper and lower extremities. Feet and hands were moist showing marked evidence of vasoconstriction. While being investigated for a scalenus syndrome a systolic murmur was found over the left subclavian artery which was transmitted into the left axilla and being a physician the patient was worried that she might have an aneurysm.

Under local anesthesia the brachial artery was exposed in the mid-arm and an 18-

gauge needle was introduced in a retrograde fashion into the vessel. With distal occlusion, 25 cc of 35 per cent Diodrast were injected rapidly into this vessel and serial films taken. These films showed no filling proximal to the junction of the axillary and brachial arteries (Fig 7A).

The same procedure was carried out a second time, this time with the Valsalva maneuver, and revealed filling at the origin of the subclavian artery and also demonstrated a small notch in this vessel immediately distal to the origin of the vertebral artery. The opaque material entered the vertebral artery and was traceable to the base of the skull (Fig 7B).

Comment Here retrograde arteriography was useful in showing that there was no aneurysm present.

Case 10—This 67-year-old woman was admitted to the Franklin Hospital because of the development of small circumscribed areas of induration with inflammation in the skin of her toes. In March of 1949 a left femoral arteriogram was performed with an 18-gauge needle, 20 cc of Thorotrast being injected at the height of a Valsalva maneuver. Occlusion of digital vessels was demonstrated (Fig 8).

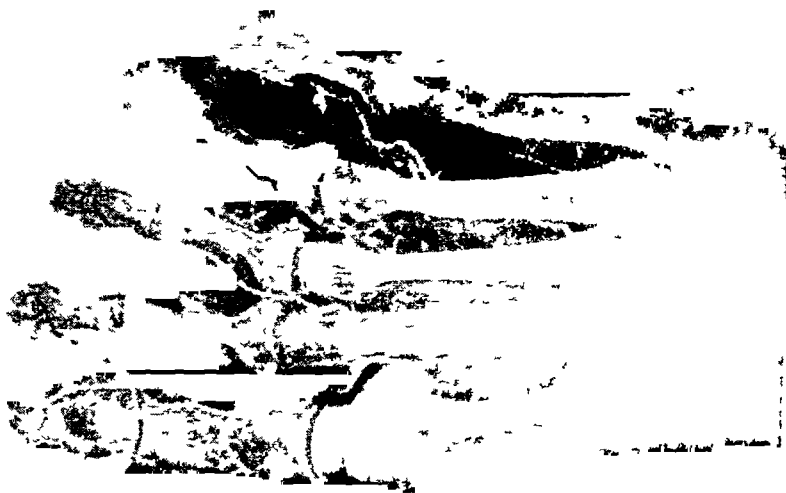


FIG 8 (Case 10)—Femoral arteriogram with Valsalva maneuver showing clear delineation of digital vessels. Note multiple areas of arterial obliteration.

Comment The use of the Valsalva technic made possible a sufficient concentration of Thorotrast in the smaller vessels so that the digital vessels could actually be visualized.

Case 11—This 32-year-old man was shot in the right upper thigh in December of 1948. Two weeks after his injury the patient was observed to have a systolic bruit and thrill over the right femoral vessel just below the inguinal ligament. Proximal occlusion of the femoral vessel caused a pulse decrease of 90 beats to 67 beats per minute.

An unsuccessful attempt to visualize the right femoral vessel was made by retrograde arteriography from the left common femoral. The right common femoral was then injected in a retrograde fashion with 30 cc of 35 per cent Diodrast, through an 18-gauge needle. Serial roentgenograms were taken beginning when the injection was half completed, and demonstrated an aneurysmal dilatation of the common femoral artery, almost at the site of the arterial puncture which filled very poorly.

THE VALSALVA MANEUVER

A

FIG 9

B

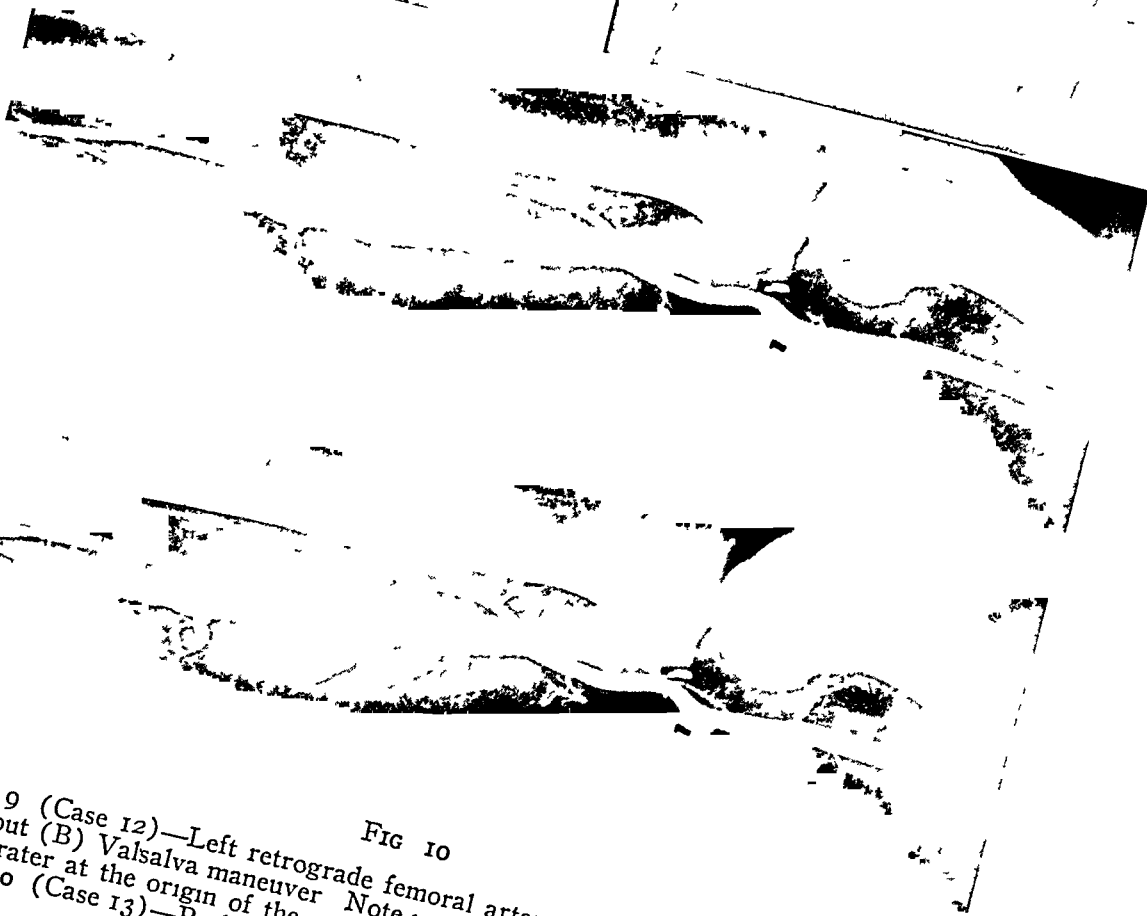
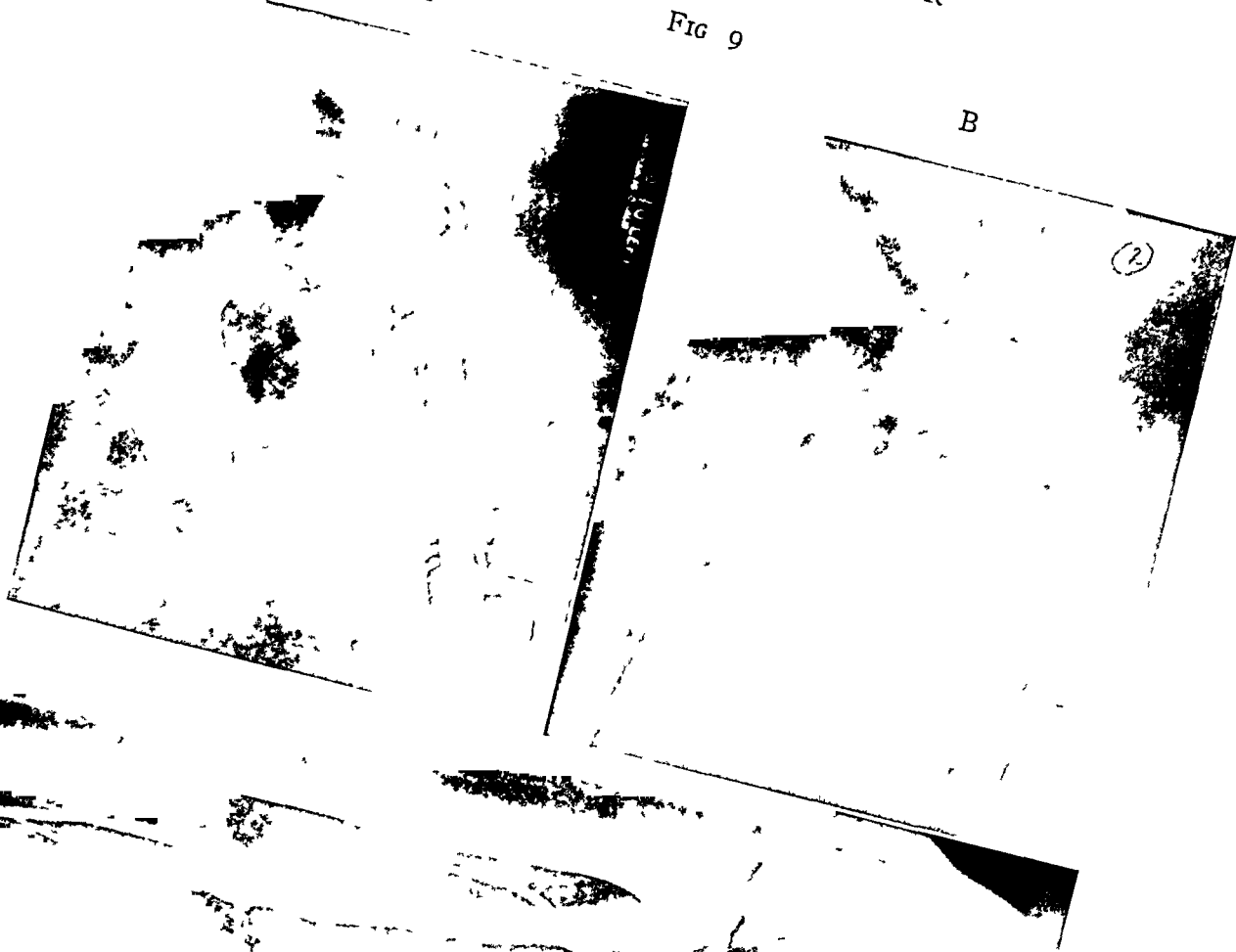


FIG 10

FIG 9 (Case 12)—Left retrograde femoral arteriograms performed with (A) and without (B) Valsalva maneuver. Note in (A) the filling of the abdominal aorta and the crater at the origin of the right common iliac artery, which is obliterated.

FIG 10 (Case 13)—Right retrograde posterior tibial arteriogram with Valsalva maneuver.

Comment This is the first case in which we were unable to demonstrate an arterio-venous fistula, and retrograde carotid arteriography probably should have been performed. Surgery demonstrated two arterio-venous aneurysms.

Case 12—This 63-year-old man was admitted to Franklin Hospital in March of 1947 because of intermittent claudication in his right leg and thigh of one year's duration. Physical examination showed a faint right femoral pulse but no pulsations distal to this point. The arterial pulsations of the left lower extremity were normal. The left common femoral artery was exposed surgically. Through a 15-gauge needle 50 cc of preheated 35 per cent Diodrast were injected in a retrograde fashion, after the blood pressure had been reduced to a low level by a Valsalva maneuver. Serial films were taken beginning when about 35 cc of the Diodrast had been injected. The same procedure was then repeated without the Valsalva maneuver. Each injection required 3 to 4 seconds for completion. In the films taken during the Valsalva maneuver, the Diodrast was seen at the level of the renal artery. The films demonstrated a filling defect with a crater in the right common iliac artery with obliteration of the lumen for $1\frac{1}{2}$ inches (Fig 9).

Comment The arteriogram was helpful in this case in locating the area of obliteration, and right lumbar sympathectomy has given marked relief.

Case 13—This 25-year-old veteran was admitted to Franklin Hospital for circulatory study in the Veterans Administration Vascular Research Project as set up by the Subcommittee on Vascular Surgery of the National Research Council. This patient had sustained a shrapnel wound resulting in two arterio-venous aneurysms, one of the right popliteal artery and one of the posterior tibial artery and vein. These were repaired by the senior author (N E F). The pulses were present in both extremities, however, the pulses in the right foot were diminished in comparison to those of the left. Arteriography had previously been attempted in an army hospital, resulting in extravasation of Thorotrast into the femoral area and subsequent development of an indurated mass in the femoral triangle. For this reason retrograde arteriography was selected.

The posterior tibial artery was exposed two inches above the medial malleolus. Inasmuch as an ordinary sharp-bevelled needle was found to lacerate the wall of the small vessel, making pressure injection difficult, a round Lindemann cannula was used. This technic may be advisable in injecting small arteries. A Valsalva maneuver was initiated and at its height 20 cc of 35 per cent Diodrast were injected in a retrograde fashion and serial films were taken, the first film being taken when the Diodrast had been half injected. Following this procedure the posterior tibial pulses could be felt distal to the point of injection. In this patient a completely normal popliteal and posterior tibial artery were demonstrated following reconstructive endo-aneurysmorrhaphy (Fig 10).

Comment In this patient it is demonstrated that it is possible to visualize the main arterial channels of the leg and thigh by retrograde injection. It is interesting to note the persistence of collaterals five years after repair of an arterio-venous fistula.

DISCUSSION

In the year 1740 there was published in Venice a treatise written in Latin "*The Works of That Most Celebrated Man, Antonio Valsalva, That Is, His Tract on the Human Ear and His Anatomical Dissections*." Through the kindness of Professor J B deC M Saunders of the Department of Anatomy, University of California Medical School, the following translation has been made from Valsalva's observations on the physio-pathology of suppuration in the middle ear.

"I say that if by closure of the mouth and nose the air contained within is compressed, then pus may be freely extruded by this act "

The Valsalva maneuver has been used in physiological experiments, both in the experimental animal and in human subjects, as a means of altering cardiovascular hemodynamics. Bruck⁶ conducted extensive studies on the cardiovascular changes produced, and refers to the Valsalva maneuver as a well-known physiological phenomenon. Wiggers⁷ has discussed the mechanism of the changes in pulse and blood pressure and in 1923 published a pulse tracing, taken with optical recording, of the alterations which took place when the intrathoracic pressure was suddenly increased. This maneuver has been used extensively by Wilkins and his collaborators^{4, 8} as a means of evaluating the sympathetic innervation in patients with hypertension. The period of forced expiration was limited to ten seconds in their cases, and chief interest was focused upon the rise in blood pressure following release of the glottis.

In the series of patients here reported the Valsalva maneuver was used chiefly to depress the cardiac output. If the intrathoracic pressure is increased for a longer period than ten seconds, almost complete suppression of the pulse can be obtained in the majority of cases, and as shown in Fig. 2, the blood pressure can be reduced to low levels. It is probably significant that the only case in this series in which it was impossible to visualize the arterial system successfully with the use of the Valsalva maneuver was Case 11. This patient had a large arterio-venous fistula, involving the right femoral artery and vein. The failure of the Valsalva maneuver to allow retrograde flow of the radiopaque material may have been due in this case to the fact that the large communication between arterial and venous systems resulted in such a rapid filling of the right side of the heart that it was impossible to reduce the cardiac output by means of increasing the intrathoracic pressure.

The Valsalva maneuver is not without danger, especially in patients with degenerative cardiovascular disease. During the period of hypotension resulting from the reduced cardiac output, there may be sufficient anoxia, both of the myocardium and of the brain, to produce irreversible changes, or even to produce intravascular thrombosis. It is possible that in Case 5, the coronary occlusion which developed a few hours after this procedure may have been due to the lowered blood pressure associated with the Valsalva maneuver. On the other hand, in patients with pre-existing hypertension, as Wilkins has shown,⁴ the hypertension following release of the forceful expiration may be sufficient to cause the rupture of some weakened segment of the arterial tree. The demonstration of radiopaque material within the walls of the dilated thoracic aorta in Case 5 can only have been due to a rupture of the intima of the aorta at the time that the radiopaque material was within the lumen.

A third possible danger in the use of the Valsalva maneuver arises from the fact that the concentration of radiopaque material within the vascular system is greater than without the use of this procedure. Special precautions should therefore be taken to prevent this material in concentrated form from reaching portions of the vascular system where it may produce injury. In Case 2 and

in Case 7, it is probable that the complications which developed resulted from the high concentration of 70 per cent Diodrast in the intracranial arteries. Although we have encountered no instances in which myocardial injury was produced by the entrance of 70 per cent Diodrast into the coronary arteries, it seems possible that with the injection of 70 per cent Diodrast in a retrograde fashion into the right or left common carotid artery, a sufficient concentration of the dye could be present in the aorta to allow some of the 70 per cent Diodrast to enter the coronary circulation.

Arteriography is not a harmless procedure, and it is our opinion that it should be used only in those cases in which the visualization of the vascular system can contribute to a better understanding of the pathological process and to the treatment, medical or surgical, in the individual case.

SUMMARY

Radiographic visualization of the vascular system requires a high local concentration of radiopaque dye. In large vessels where the volume flow of blood is great, the injected dye is rapidly diluted and visualization is difficult. Temporary diminution of the cardiac output by means of the Valsalva maneuver (forced expiratory effort against the closed glottis) permits injection of radiopaque material into a major vessel containing relatively stagnant blood. With subsequent return of blood velocity, which occurs when the patient exhales, this material traverses the arterial system as a bolus in sufficient concentration to be visualized in successive roentgen ray films. This technic has been used in 13 patients, by both direct and retrograde arteriography for visualization of the thoracic and abdominal aorta, as well as of the major peripheral arteries. Satisfactory visualization was obtained in ten of the 13 cases. The dangers of the successive hypotension and hypertension produced by this maneuver are emphasized.

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THE VALSALVA MANEUVER

DISCUSSION—DR REGINALD H SMITHWICK, Boston I have not had any experience with the Valsalva maneuver in arteriography, but Dr Wilkins and I have been very much interested in it as a means of studying reflex control of blood pressure in normotensive and hypertensive patients

I would like to show one slide because I think it will illustrate very clearly the hemodynamics that are concerned in this maneuver which Dr Freeman has taken advantage of in arteriography

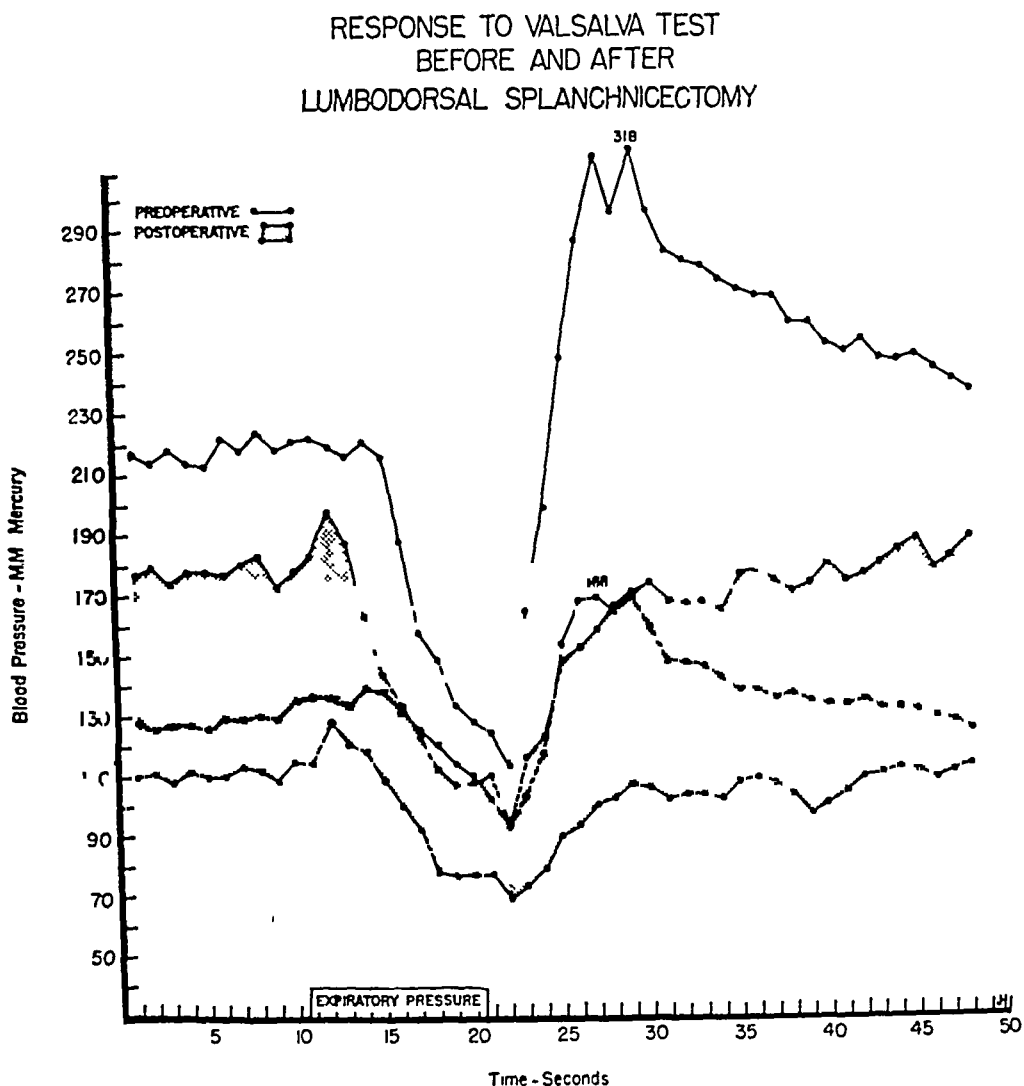


FIG 1

In our studies we have made continuous records of blood pressure by means of intra-arterial recordings with a Hamilton manometer. The above figure is an illustration of a Valsalva maneuver as we carry it out in the study of hypertension. The solid line is the preoperative observation, and the shaded chart indicates the effect of a thoracolumbar splanchnicectomy upon blood pressure.

During the ten-second period of forced expiration against a positive pressure of 40 millimeters of mercury, as Dr Freeman has indicated, the blood pressure falls precipitously, as shown here, because of decreased venous return and cardiac output.

When the expiratory period ceases the blood pressure falls for one pulse beat after the period of expiration, and then during the succeeding five pulse beats over a period

of about five seconds there is this extraordinary overshoot of blood pressure to very high levels. In this case it went to 318/168. It shows that this maneuver can result in tremendous overshoots of blood pressure, and may be hazardous.

Following the denervation of a large vascular area, as shown by the tracing the blood pressure falls in a similar fashion during the Valsalva maneuver, but after that there is a very much less precipitous rise in pressure, which in thoroughly denervated patients gradually comes up to the previous base line but never overshoots it. Thus we regard as one of the very important physiological effects of extensive sympathectomy and believe it to be of considerable therapeutic value in the management of hypertension.

I might say that these same sort of responses may be seen in patients with coarctation of the aorta, and they may have marked overshoots as judged by the Valsalva maneuver, as many hypertensive patients do. That, incidentally, is the rationale for our having operated upon a series of patients with coarctation of the aorta that are beginning to get into difficulty in the older age group. We hope that by modifying these reflex variations in blood pressure, the progress of cardiovascular disease will be slowed. So far, the patients seem to have done very well, although we have only a small series and some cases have been observed for only a short period of time.

The abolition of the sharp overshoot following the Valsalva maneuver can also be accomplished by means of sympatholytic drugs. I mention that simply because it might be that if this period is hazardous in arteriography, the use of a short-acting sympatholytic agent given prior to the maneuver might eliminate some of the complications Dr. Freeman has mentioned. It might also not in any way interfere with the success of the arteriography, and, because of the slower rise in blood pressure, might give a longer period of time to expose the films.

DR. NORMAN E. FREEMAN, San Francisco: I want to thank Dr. Smithwick for his very valuable suggestion. I believe his suggestion of the use of some sympatholytic drug to prevent the marked overshoot is an excellent one.

In general, I have emphasized the hazards of this maneuver because of the fact that it is a dangerous procedure, and that we hesitate to employ it, especially in the older age group. I feel, however, that in some cases it is the only way in which an effective arteriogram which will determine therapy can be obtained.

Of the total number of cases in which this maneuver was used—I think there were about 17 cases—I have emphasized the three complications we have had, two in which the dye reached the intracranial circulation, and one who had an extravasation of the dye into the walls of the aorta. The other 14 cases showed no undesirable side effects.

In general, I think it is advisable to expose the artery, since this material is injected very rapidly by an assistant, and it is wise to have the needle connected to the syringe by means of a short section of rubber tubing to prevent the needle from being dislodged by the forceful injection.

SURGICAL TREATMENT OF INSIDIOUS THROMBOSIS OF THE AORTA*

REPORT OF TEN CASES

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THROMBOSIS OF THE AORTA, insidious in nature, and not the result of so-called saddle embolus, is a disease rarely observed and reported. In the last 20 months, ten patients have been seen with this condition. Although reports in the literature of *embolic* obliteration of the bifurcation are numerous, those of *thrombotic* of the terminal aorta are noticeably few. Little effort has been made to differentiate between the two entities despite the fact that both were described as early as 1814 by Graham.¹

A case reported by Barth² in 1848 is one of the first in which *insidious obliteration* of the aorta was considered. In this patient, a cylindrical thrombus developed and extended from the superior mesenteric artery to the aortic bifurcation, leaving a narrow channel for the flow of blood. The author observed that no circulatory changes were manifest at onset, but numbness in the lower extremities and intermittent claudication became apparent at a later date.

In most instances, reports have been made of groups of patients with embolism, with or without secondary thrombosis, in addition to those having primary thrombosis of the aorta. In 1898, Welch³ collected all the reported cases of thrombosis and embolism of the terminal aorta. In this group of 59, 14 were considered to be thrombotic, and of these, seven were primarily thrombotic. In 1923 this lesion was again reported by Leriche⁴. In 1940, he described the symptom complex and diagnostic criteria, and reported five cases in which the diagnosis was clearly substantiated at operation.⁵

In 1943, Greenfield⁶ reported 156 cases of thrombosis and embolism of the abdominal aorta, including five of his own, and the group previously reviewed by Welch. No clinical differentiation was made between the two conditions. Holden (1946)⁷ reported two cases of thrombotic occlusion of the aorta treated by sympathectomy with good results. Recently (1948), Leriche⁸ published a classic description of the syndrome of obliteration of the terminal aorta by thrombosis and its differentiation from occlusion by an embolus.

ETIOLOGY AND PATHOLOGY

The bifurcation of the aorta is the site at which atheromata are most likely to develop, and at which arteriosclerosis is intensified, often with the production of ragged, calcified, ulcer-like areas in the intima. Thus it is a susceptible point for the formation of a thrombus with ultimate narrowing.

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and constriction of the lumen. Gross and Philips⁹ in 1940 pointed out that thrombosis of the abdominal aorta may occur in the presence of an ulcerated arteriosclerotic plaque, a dissecting aneurysm, arteritis, or congenital narrowing of the aorta. Why it is not a more common observation at autopsy in patients with severe arteriosclerosis at this site is not known.

As Leriche⁸ has pointed out, the thrombosis may be progressive in that it frequently arises in the iliac arteries and propagates upward to eventually obliterate the aortic lumen at the bifurcation and just above that point. Death frequently results from hypertensive cardiovascular disease and uremia which follows the progression of the thrombus up to and above the origin of the renal arteries.



FIG 1, Case 2—Resected bifurcation of the aorta showing thrombus

Examination of the excised bifurcation of the aorta in one of the cases reported here revealed findings typical of this disease (Fig 1). The specimen consisted of a segment of the aorta and common iliac arteries, 5 cm long, occluded by a thrombus. There was calcification in the wall of the aorta and in the thrombus. Microscopic examination showed marked intimal proliferation in both the aorta and the iliac artery. There were large calcified plaques between the media and the intima with areas of degeneration of the media.

SYMPTOMATOLOGY

The predominant symptoms in the patients observed were pain in the hip and legs, easy fatigability, and intermittent claudication in the lower extremities (Table I).

Next to pain, the most pronounced symptom was easy fatigability and weakness in the thighs and legs when walking. Loss of sustained erection was frequently an additional symptom.

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The average duration of symptoms in the ten cases was seven years, although the progression of symptoms and physical changes was not identical in each patient. The two patients with the most severe symptoms and pronounced trophic changes developed them within the shortest period of time.

DIAGNOSIS

The diagnosis may be made from the history and physical examination. The most common observation, and present in all but one instance, was the absence of peripheral pulsations, including the femoral, in the lower extremities. Of equal significance was the absence of pulsation in the abdomen below the umbilicus.

Trophic changes, such as thickening and roughening of the nails, and loss of hair were noted. Moderate pallor on elevation of the lower extremities

TABLE I

SYMPTOMATOLOGY							
CASE	PAIN	PAIN IN HIP REGION	EASY FATIGABILITY OF LOWER EXTREMITIES	INTERMITTENT CLAUDICATION	LOSS OF SUSTAINED ERECTION	BURNING PAIN	DURATION OF SYMPTOMS IN YEARS
1	+	+	⊖	+	NP	+	7
2	⊖	NP	+	+	NP	+	2
3	⊖	NP	+	+	+	NP	3
4	+	⊖	+	+	+	NP	5
5	+	NP	⊖	+	+	NP	5
6	⊖	+	+	+	+	NP	10
7	+	NP	⊖	⊖	NP	NP	10
8	+	+	+	⊖	+	NP	10
9	+	NP	⊖	⊖	NP	NP	5
10	NP	NP	+	+	NP	NP	12

+ SYMPTOM PRESENT
 ⊖ ORIGINAL SYMPTOM
 NP SYMPTOM NOT PRESENT

TABLE II

INSTRUMENTAL EXAMINATION OF LOWER EXTREMITIES						
CASE	⊖ BALLISTO CARDIOGRAM	SKIN TEMPERATURE	OSCILLOMETRY			
			RIGHT KNEE	LEFT KNEE	RIGHT ANKLE	LEFT ANKLE
1		VERY HIGH	0.5	1.0	F	0.5
2	+	DIMINISHED	F	0	0	0
3	+	NORMAL	1.5	1.0	1.5	1.0
4	+	DIMINISHED	0	0	0	0
5	+	NORMAL	1.5	1.5	0.5	0.5
6	+	NORMAL	0.5	1.0	F	1.0
7	+	DIMINISHED	0	0		AMP
8	+	NORMAL	0.5	0	0	0
9	+	DIMINISHED	0	0	0	0
10	+	DIMINISHED	1.5	1.5	1.0	1.5

⊖ + CONSISTENT WITH CONDITION
 F FLICKER OF OSCILLOMETER NEEDLE
 0 NO PULSATION OF OSCILLOMETER NEEDLE AT ANY PRESSURE

TABLE I—The predominant symptoms of 10 patients with thrombosis of the bifurcation of the aorta

TABLE II—Instrumental findings on 10 patients with thrombosis of the bifurcation of the aorta

was another noticeable finding. Rubor and cyanosis were observed in some instances with the extremities in a dependent position. Gangrene and atrophy were usually absent, and were seen in only three of our patients. In the others, the absence of physical changes which might be expected with obliteration of such a large and important component of the circulatory bed is singularly significant. This is probably accounted for by the insidious nature of the disease and the development of abundant collateral channels.

Thrombosis of the aorta is easily differentiated from embolus to the terminal aorta. In the former, the onset is unsuspected because the symptoms are mild, while in the latter, the onset is sudden and the pain severe. In both conditions the pulsations of all vessels below the umbilicus are usually absent. Changes resulting from severe circulatory insufficiency are noted immediately in the lower extremities following embolus. Coldness to touch, hypesthesia, frequently anesthesia, and abnormal pallor become apparent immediately. In

chrombosis, these changes appear late, often years after the onset of symptoms. In both conditions, unless treatment is instituted, gangrene and ulceration are the ultimate outcome, occurring in a period of days in patients with emboli after years in those with thrombosis.

Instrumental observations yield useful information and are included in this study to substantiate clinical evidence, but are not essential for diagnosis. Skin temperatures, oscillometry and ballistocardiograms were recorded on each patient. Ballistocardiograms of a normal person and of a patient with thrombotic obliteration of the bifurcation of the aorta are presented for com-

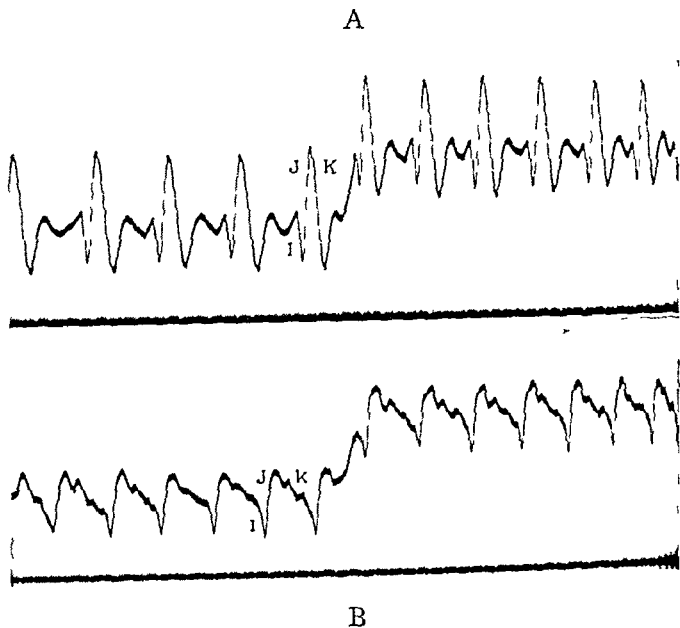


FIG 2—Ballistocardiogram of A, normal individual, and B, patient with thrombotic obliteration of the bifurcation of the aorta (See footnote for explanation of wave changes)

The Nickerson modification of the ballistocardiograph¹⁰ was used in this series. It has a low, natural undamped frequency of 15 cycles per second, and an incorporated critical damping mechanism. Only the deflections resulting from the initial impacts are recorded, the remainder, occurring subsequent to the ventricular systole, being 'dumped' out. This renders the Nickerson apparatus particularly suitable for the study of patients with thrombosis of the bifurcation of the aorta or coarctation of the aorta, since it is in these initial impacts that aberrations from the normal occur.

There are only three waves which are of significance in a ballistocardiogram of this type. The first of these (I wave) is from a footward recoil following the headward ejection of blood during ventricular systole. A greater headward deflection (J wave) then follows as the column of blood in the heart, ascending aorta, and pulmonary artery is first decelerated. A footward force, producing the K wave, follows and is due to the impact of the column of blood in the descending aorta against the peripheral resistance. It is in this latter wave that an abnormality occurs which appears to be characteristic of patients with thrombosis of the terminal aorta. In a normal individual, the slope of the curves described above approaches 90 degrees. The I wave is shallow, and the J and K waves are approximately equal in slope and magnitude. When the lumen of the terminal aorta is narrowed or obliterated, however, the column of blood in the descending aorta meets a resistance earlier and is diverted sagittally through branches and collateral channels proximal to the obstruction. The K wave therefore does not approach the baseline sharply, but tapers off irregularly, forming an angle of much less than 90 degrees.

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parison (Fig 2A,B See footnote) The findings obtained on each patient by these examinations are presented in Table II.

Roentgenographic examination of the aorta in the cases so examined frequently showed extensive calcification In two instances, an aortogram demonstrated the exact level of the site of obliteration (Figs 3 and 4)



FIG 3, Case 3—Aortogram showing obliteration of the aortic lumen at the level of the second lumbar vertebra



FIG 4—Case 10—Aortogram (retouched) showing obliteration of the aortic lumen at the level of the first lumbar vertebra The right renal vessels are seen, but the left renal vessels are not visualized Collateral circulation is greatly increased

PROGNOSIS

With any method of treatment, the prognosis is grave, due to the underlying nature of the disease Death usually results from the complications of arteriosclerosis coronary occlusion, uremia, or the effects of hypertension after the thrombus has extended up to and above the renal arterial orifices It may result from gangrene and infection in the extremities However, certain measures are frequently of value in improving the circulation and in relieving symptoms

TREATMENT

Treatment is based on the tenets set down by Leriche He has stated^{5, 8} that the ideal treatment would be to resect the obliterated zone and to bridge

that time he had also developed an ulceration of the right leg, which was extremely painful and had progressively enlarged

The amputation stump of the left leg was well healed. The right foot and toes became pale on elevation, and ruborous on dependency. An ulceration was present on the right leg. Pulsation of the abdominal aorta could be felt, but no pulsation of any vessels were palpable below the umbilicus.

Treatment A right lumbar sympathectomy was performed. The skin surface temperatures increased, but there was very little relief of pain in the area of ulceration. The patient left the hospital before treatment was completed.

Case 8—R C, a 60-year-old white male, was seen on August 25, 1948. For 10 years he had suffered from cramps in the right leg on walking. One year prior to examination, his symptoms became markedly exaggerated following an illness due to food poisoning. The claudication became so severe that he was able to walk only 10 to 12 steps before developing pain on the right. He noticed back pain and loss of power of sustained erection. One month before examination he developed small, gangrenous ulcers on the third, fourth, and fifth toes of the left foot, which had failed to heal.

Numerous petechiae were present in the skin on the left foot and ankle. The foot became markedly blanched on elevation and ruborous on dependency. Similar color changes were present in the right lower extremity, but to a lesser degree. Trophic changes were present in the skin of both feet.

Treatment A bilateral lumbar sympathectomy was performed with removal of the first, second and third lumbar ganglia. Exploration of the abdominal aorta revealed it to be thrombosed from the bifurcation of the iliacs to the level of the inferior mesenteric artery. Since calcification of the arterial wall was intense, resection of the thrombosed segment was not performed.

The ulcerations on the foot healed and the areas of gangrenous ulceration disappeared. The patient became ambulatory, and was able to return to his work, using only a cane to aid in walking. Five months after operation, he died suddenly from what was presumed to be a pulmonary embolus or coronary occlusion. No autopsy was obtained.

Case 9—G L, a 60-year-old white male, was seen on June 10, 1948. He gave a history of claudications in both legs for 5 years, with greatly increased difficulty during the 6 months preceding examination. Numbness, redness and increasing pain in the right foot had also been noted. There were slight trophic changes in the nails and hair of the toes. There was pallor of the right foot on elevation, and rubor on dependency. All arterial pulsations were absent in the extremities, except for a faint femoral pulse on the right.

During five months of observation he developed progressive trophic changes in the skin of his right and left feet, and an ulcer on the third right toe. On re-examination he was found to have no arterial pulsations below the umbilicus.

Treatment A bilateral lumbar sympathectomy was performed with removal of the first, second and third lumbar ganglia. Palpation of the abdominal aorta revealed it to be thrombosed and involved in a severe atheromatous process.

Following operation, the ulceration on the tip of the third toe healed promptly and the pregangrenous areas on the foot resolved. The patient was able to return to work and has experienced greatly increased tolerance for exercise.

Case 10—F D, a 58-year-old white male, was seen on December 29, 1948 complaining of tiredness, weakness, claudication, and easy fatigability of his legs on activity of mild degree. Those symptoms had gradually increased in severity for 12 years.

Examination revealed no trophic changes or skeletalization of the extremities. No abnormal color changes were present on elevation and dependency. No arterial pulsations could be palpated below the femoral artery, but definite femoral pulsations were present bilaterally. Pulsations of the abdominal aorta were present but iliac pulses were not perceptible.

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An arteriogram of the aorta revealed a block below the right renal artery. There was no filling of the left renal artery, and no kidney function could be demonstrated on the left (Fig 4).

Treatment This patient has been advised to have a bilateral sympathectomy.

SUMMARY

The diagnostic criteria, etiology and pathology of insidious thrombosis of the aorta is presented.

The histories of ten patients are presented, and their treatment described.

A review of the literature reveals a paucity of case reports, but it is believed that this disease is more prevalent than is assumed.

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DISCUSSION—DR EMILF HOLMAN, San Francisco. I should like to report on four patients with obstructive calcification of the terminal aorta upon whom we have operated in the last ten years. The first one was a young woman of 45 who came to us in 1940 and who presented at operation a very thick plaque at the bifurcation without evidence of calcification, but producing complete obstruction. At the present time, she shows beginning calcification in this short segment, the only part of her body where we can demonstrate it. It is an interesting condition, probably preliminary to the

development of extensive calcification seen in three other patients. This patient had a bilateral sympathectomy and is greatly improved so far as the predominant symptoms are concerned, one of which was the constant realization that she had a very vigorously beating abdominal aorta, a phenomenon which really bothered her a great deal. Since the sympathectomy this has disappeared. Also, numbness of the extremities, extending well up to the pelvis following the slightest exertion, has disappeared.

The second patient, 56 years of age, presented herself with an indolent ulcer of the heel incident to peripheral ischemia due to calcification of the terminal aorta. This has finally healed nine months following bilateral sympathectomy.

A third patient of 65 presented the usual symptoms shown by Dr. Elkin's patients—namely, easy fatigability and calf pain on the slightest exertion. This patient also had extensive obliterative calcification of the terminal aorta and peripheral ischemia, for which a bilateral sympathectomy was done, with great improvement. Whereas before operation fatigue and pain developed after walking ten or 20 feet, she now can walk a block and more with comfort.

A fourth patient who also presented the same phenomena detailed by Dr. Elkin was operated on by Dr. Gerbode of our clinic who also performed bilateral lumbar sympathectomy with marked improvement. It is our opinion that resection of the calcified aorta, as advocated by Leriche and his co-workers, is too hazardous for the gain obtained, and that bilateral lumbar sympathectomy will provide as much improvement as can be expected.

DR MIMS GAGE, New Orleans, La. I have enjoyed Dr. Elkin's paper very much and consider it most appropriate because we are seeing an increasing number of patients with Leriche's syndrome.

I recently saw a dentist less than 50 years old, who could not continue practicing because of the weakness of his legs. He had typical Leriche's syndrome—weakness of the legs, claudication in the calf muscles and increasing impotence. A bilateral sympathectomy was done. The aorta was not ligated because of the extensive arteriosclerosis.

I would like to call attention to the same type of syndrome in patients who have pronounced arteriosclerosis of the abdominal aorta with tortuosity but no thrombosis and with pulsations in the aorta, iliac and femoral arteries. The pain and discomfort in the lower extremity may be due to sympathalgia, i.e., irritation of the aortic sympathetic plexus from the arteriosclerotic aortitis. It is surprising how many of these patients have systolic murmurs over the bifurcation of the aorta as well as over the external iliacs. This, of course, is due to segmental narrowing of the aorta and iliacs by arteriosclerotic plaques. Some of these patients have minor symptoms of the Leriche syndrome, whereas others have no symptoms. It will be most interesting to observe these patients over periods of time to see if the syndrome so accurately described by Dr. Elkin develops in them.

We should all be on the alert for these cases, and I would strongly advocate that we listen to the aortic and iliac arterial sounds in all patients whom we examine.

DR NORMAN E. FREEMAN, San Francisco. We also have encountered patients with absence of pulses below the groins, and we have been able to visualize these arteries by means of retrograde arteriography, using the carotid approach. I have one slide to illustrate the fact that occasionally it is possible to have very marked obliteration and still have a small lumen.

(Slide) This patient, a man of 68, had absent pulses in both femoral areas. There was marked distortion of the aorta with almost complete occlusion. However, there is a small lumen present, and apparently the dye is able to get down through the collaterals. The middle sacral artery fills, and the left iliac artery fills fairly well from

the right side, the other vessels are also filling. There is marked obstruction of the aorta just below the origin of the renal arteries, and yet both femorals fill through collateral vessels.

DR FREDERICK L. RICHLETT, San Francisco: This claudication business in the thigh might well be due to shutting off the lumbar segmental artery. In cutting out the coarctation of the aorta, the segmental arteries are divided. It might be well to preserve them. So in thrombosis of the aortic bifurcation segmental arteries are shut off.

I think a sympathetic innervation would be much more to the point.

QUANTITATIVE STUDIES ON THE TIME FACTOR IN ARTERIAL INJURIES¹

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THE PERIOD during which an extremity, deprived of its major source of blood, remains ischemic is a factor of particular importance influencing the chance for survival upon restoration of its circulation. The disappointing results which were obtained in the treatment of arterial injuries in the leg as observed in World War II could be attributed to some extent to the considerable "time lag" or period elapsing between wounding and receiving surgical attention. Long periods of ischemia with necrosis of tissue associated with thrombosis of small arteries may produce a leg that is beyond recovery. Progress in the field of early definitive surgery was disappointing in World War II^{1,3}. The number of immediate anastomoses of severed arteries was relatively small although an advance was made in this field as compared with the number done in World War I^{4,6}. The incidence of necessary amputation after femoral or popliteal injury treated by ligation was high^{7,8}. In the experience of one of us, gangrene of the leg occurred after ligation of the femoral or popliteal arteries in 70 per cent of patients⁹. It is true that not much more than ligation was possible or advisable in many instances. It must be said, however, that a vast field for improvement in the management of arterial injuries remained at the end of the war. In retrospect, several shortcomings in the overall management of vascular casualties seem to stand out after analysis of the recorded experience. In the first place it was not fully appreciated that anastomosis of the artery was essential for good results, although Blakemore strongly advocated the use of his non-suture method in battle casualties¹⁰. A program whereby casualties with arterial wounds might be detected early and receive priority treatment was not attempted. The general lack of surgical experience with arterial anastomosis in the absence of a highly satisfactory technic applicable to all cases also contributed to the unsatisfactory end results. In a previous work we have studied several methods of arterial anastomosis in experiments in which the survival of the dog's leg depended upon one artery which had been interrupted and rejoined. The results of these experiments exonerate all types of intima-to-intima anastomosis as an important primary cause of gangrene and failure in the salvage of limbs. Our findings in these experiments performed on dogs indicated that approximately 80 per cent of legs depending on a single anastomosed artery will

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survive and be restored to nearly normal under clean wound conditions if there is no appreciable period of ischemia or "time lag"¹¹

In the present work we wish to present a study of the "time factor" in acute arterial injuries. The ideal time for restorative surgery is considered to be under six or eight hours⁴. Not much hope has been held for the success of anastomosis procedures after this time insofar as salvaging the leg is concerned. Clinical data on the survival of human legs after various periods of acute ischemia followed by restoration of the blood supply by anastomosis is insufficient. Furthermore, the variation in the extent of the wound and the amount of functioning collateral circulation remaining in the clinical case makes an accurate evaluation of the time factor difficult as a single item. The following experiments were projected to obtain data on the survival of extremities in a series of dogs subjected to varying periods of acute ischemia under conditions which have been sufficiently standard to have significant validity.

EXPERIMENTAL METHOD

The procedure to be described was carried out on 63 dogs. Immediate mortality and death from causes not related to the leg left 57 animals for evaluation. Three separate groups of dogs were subjected to periods of acute ischemia as follows: Group I for 1 to 6 hours, Group II for 12 to 18 hours, Group III for 24 to 30 hours. A standard procedure for producing arterial injury and acute ischemia and for restoration of the circulation was used in all experiments.

The arterial injury and period of ischemia. Acute arterial injury was produced by utilizing a modification of the Halsted-Reichert leg transection replantation procedure^{12, 13}. After an especially careful skin preparation, a transection of the soft tissues of the leg was made in the mid-thigh region of anesthetized dogs. The femur, the femoral and sciatic nerves, the femoral artery and femoral vein were preserved. Anatomical replantation of the leg was then performed. At the end of this procedure the femoral artery was ligated and the vessel was effectively occluded throughout the desired period of ischemia. This preparation cuts off the main artery of supply and all collateral routes for blood via the soft tissues. Although a small amount of blood may reach the distal extremity beyond the transection by way of the medullary cavity of the femur, it is insufficient to sustain life in the leg. Previous work by Reichert¹³ and by Callow and Welch¹¹ has shown that ligation of the femoral artery in this transection replantation preparation is followed by gangrene of the leg in 100 per cent of animals. This work established the controls for the present experiments.

During the period of ischemia the wound was completely closed and the leg was encased in a plaster of Paris splint for immobilization and avoidance of contamination. During the ischemia the animals were kept at ordinary room temperature at 70 degrees to 80 degrees Fahrenheit.

The restoration of circulation. At the conclusion of the ischemic period, the ligated femoral artery was exposed under aseptic conditions. It was then

prepared for anastomosis by trimming off a cuff of adventitia. The ligated portion of the femoral artery was then excised. Thrombosis at the site of ligation was observed in less than 20 per cent of the arteries and when found was confined to the proximal segment. A good pulsating blood flow was demonstrated at the proximal end of the artery before anastomosis. The continuity of the femoral artery was restored by inserting an arterial graft between the severed ends. The suture technic was employed in all experiments. The graft was held in place by stay sutures and the anastomosis was completed by a continuous lock stitch. The technic of arterial graft was especially useful in these experiments since it permitted anastomosis with minimal tension in this situation in which a portion of the femoral artery had been excised. The use of a graft or bridging procedure is essential in the majority of clinical arterial wounds because extensive injury to the vessel involves loss of vessel substance making direct end-to-end suture difficult and hazardous. The application of arterial grafts to the problems of arterial injury was suggested to us by the recent work of Gross and his associates¹⁴. Autografts from the opposite femoral artery were used in 16 per cent of our experiments. Fresh homografts taken from other dogs were used in 24 per cent of the anastomoses and homografts preserved for varying periods were used in 60 per cent. These preserved or "bank" homografts were stored in a fluid medium at temperatures several degrees above freezing for as long as three weeks before they were used. Anticoagulants were not administered in these experiments either during operation or in the postoperative period.

During the course of the long transection replantation procedures intravenous fluids along with transfusions of whole blood were given. An initial dose of 300,000 units of penicillin was administered prior to operation and was continued with a daily dose of 150,000 units for 7 to 14 days. At the restorative operation wounds were completely closed and no dressings were applied.

EXPERIMENTAL FINDINGS

The experiments conducted allow observations upon three aspects of the problem of arterial injury: (1) the survival of ischemic legs after restoration of circulation, (2) the effectiveness of femoral artery grafts as a method of anastomosis, and (3) the late functional results in legs salvaged after different periods of ischemia.

Influence of Periods of Ischemia on Leg Survival Group I. The legs of 21 dogs were transected and reimplanted using the arterial graft anastomosis after a period of ischemia ranging from one to six hours. There were an approximately equal number of animals operated at the extremes of time, i.e., one and six hours. In only two animals was the leg lost, representing a 90 per cent salvage rate for this period of acute ischemia (Table I).

Group II. Of the 26 animals whose legs were transected and maintained ischemic for intervals ranging from 12 to 18 hours, 13 lost their legs. There

were approximately an equal number of animals operated at the extremes of time in this group. The rate of leg survival was, therefore, 50 per cent for the group of animals of this ischemia period.

Group III. Ten animals did not have a restoration procedure performed until after 24 hours had elapsed. Only two viable extremities were obtained, a survival rate of 20 per cent in this group. It did not seem profitable to explore the late range of this 24 to 30 hour time period in more than two of the ten animals, in view of the findings in the first eight dogs, which were done after 24 to 26 hours of ischemia. Results in these first animals demonstrated at once that the upper limit of time lag had been approached. The two legs which survived were those of dogs with ischemia for 24 and 25 hours respectively.

The legs of the dogs in all groups were pulseless and cold during the ischemic period. Skin temperatures approached that of the room in which they were exposed. The ischemic part of the leg near the transection line in the thigh was noticeably warmer than the more distal parts of the lower leg and foot since it was warmed by the adjacent vascularized tissues of the thigh.

TABLE I—*Restoration of Circulation after Acute Ischemia*

Period of Acute Ischemia	Experiments	Legs Survived	
	Number	Number	Percent
Group 1 (1 to 6 hours)	21	19	90
Group 2 (12 to 18 hours)	26	13	50
Group 3 (24 to 30 hours)	10	2	20

The skin coloration varied from a marked pallor to deep cyanosis. In Groups II and III having prolonged ischemia there was a firmness and inelasticity of the muscles which was accompanied by resistance to passive motion resembling rigor mortis.

After anastomosis had been completed, the legs became warm, the color improved and other evidences of restored circulation appeared. Usually the temperature of the operated leg rose several degrees above that of the other side. The mean rise in skin temperature was 14.5 degrees Fahrenheit at the calf as determined by a surface pyrometer. The superficial veins of the leg became obviously distended. In 80 per cent of the restored legs the pulse of the anterior tibial artery was immediately palpable at the ankle. The legs of the animals in Group I were of normal size immediately following restoration while those legs in Group II and Group III presented a moderate to marked tense swelling involving the muscular tissues throughout the extremity. In the transected replanted limbs of all groups there was a progressively increasing edema. The swelling reached a maximum in the one to six hour group on about the fourth day. On about the sixth postoperative day the edema began to subside and usually it had largely disappeared by the ninth day. Reichert has shown that the disappearance of the edema accompanies the regeneration of lymphatics across the transection.¹³ In the two longer

ischemic periods there was a more rapid increase in the edema so that after 24 hours it was marked and maximal on the third day. Several days more were required for its subsidence than in the one to six hour group of animals. When wound infection was present disappearance of edema was further delayed.

Discussion of Leg Failures The nature of the experimental procedure invited a high incidence of wound complications. The long operating time which was divided into two stages and the prolonged periods of ischemia both contributed to complications. The importance of the interval of ischemia was evident when the rate of per primum healing was examined. Sixty-two per cent of the wounds in dogs' legs subjected to only one to six hours of ischemia healed per primum while the rate in those subjected to 12 to 18 hours was 14 per cent. In those having 24 and more hours of ischemia no wound healed without complication. The extensive operative wound and the presence of ischemic tissue offered an unequalled opportunity for bacterial invasion. Positive bacterial growths were obtained from 47 per cent of the wounds that were cultured at the time of the restorative procedure in spite of all precautions used in handling these animals. None of the cultures yielded *Clostridia*.

TABLE II—*Analysis of Failures after Restorative Surgery*

Ischemic Period	Experiments	Total Failures	Graft Failures		Wound Complications (Intact Graft)
			Primary	Secondary	
1 to 6 hours	21	2	0	2	0
12 to 18 hours	26	13	1	10	2
24 to 30 hours	10	8	2	3	3
All periods	57	23	3	15	5

or anerobic *Streptococci* and none of the legs failed because of gas gangrene. Penicillin therapy greatly reduced infection in these wounds and it is possible that without it these ischemia experiments could not have been investigated, using the present technic.

The proximate cause of leg failure in 18 out of the total 23 was some accident that befell the arterial graft used to restore the circulation. The other five failures were the direct results of wound complications at the transection site.

In Table II an analysis of the findings in legs that failed has been tabulated. The majority of the graft failures were found to be secondary to wound infection with deep abscesses and dehiscence. Thrombosis of the graft perforation of the graft by erosion, or disruption of the anastomotic suture line were variously found. There were only three instances of primary graft failure, all of these had intraluminal thrombosis. This low incidence of primary thrombosis in the graft augurs well for their use, especially since anticoagulants were not used.

It was found that the muscle mass at the line of transection in the jeopardized portion of the extremity invariably succumbed first to the effects of

ischemia This was due in part to the division which the transection effects of the small vessels usually supplying these muscles from above The earlier death of these tissues, however, was not related to this factor alone, since dogs in Group I sustained the lack of this source of blood as evidenced by the rate of per primum healing and normal recovery of the legs in this group It is probable that tissue necrosis at this level proceeds at an accelerated rate because of the higher local temperature As the time of ischemia was extended, the degree of tissue necrosis was reflected in the greatly increased incidence of wound complications that were followed by leg failure This finding can be explained satisfactorily only on the basis of degeneration of tissue to a point beyond which recovery was not possible after restoration of the circulation via the femoral artery

The ischemic limbs of dogs in Groups II and III which were examined at post mortem showed grossly a softening of all the muscles, which was most evident just distal to the transection line In those of the 24 to 30 hours group with far advanced changes there was actual liquefaction of the muscle tissues in the vicinity of the transection In addition, liquefaction was observed to occur in the central portion of the anterior tibialis muscles These findings are similar to the characteristic pathologic changes of early Volkmann's ischemic contracture as Griffiths has pointed out^{15, 16} The presence of these far advanced alterations in the muscular tissue indicated that the time limits of ischemia for leg survival imposed by tissue necrosis had been approached in the time period of 24 to 30 hours during which there had been deprivation of the circulation

It may be speculated that thrombosis in the small end arteries supplying the muscle initiated, or simultaneously accompanied, muscle tissue death and that inadequate blood reached these tissues after restoration of the femoral artery Histological tissue studies of these animals' legs are in progress

Arterial Graft Anastomosis The requirement for anastomosis without tension in arterial injury in which excision or loss of some part of the vessel generally occurs is fulfilled by the arterial graft method This technic is superior to the vein graft method in a number of respects We believe that it is easier to perform than the non-suture vitallium tube vein graft technic of Blakemore, Lord and Steffen The artery graft is a sturdier bridge and does not result in the narrowing of the lumen that is unavoidable when metal cuffs are employed If autogenous grafts were an absolute requirement the disadvantage of the arterial graft technic for patients would be obvious Suitably sized fresh autografts cannot be taken from the human subject without danger of impairing circulation to the part supplied The development of a "bank" for arteries removed from cadavers as suggested and utilized by Gross, however, is a practical solution to this problem The experimental conditions in the transection-replantation wound have subjected these grafts to a rigid test In one dog in the 12 to 18 hour group which had an extensive dehiscence of over half of the tissues at the transection site which left the femoral sheath

structures suspended without support, the artery graft continued to function and to supply satisfactorily the distal leg until slow healing by granulation took place. In Fig 1 a roentgenogram of the injected arterial tree demon-



FIG 1—Arteriogram in an animal sacrificed at four months showing a functioning preserved arterial homograft. Arrows indicate the site of the graft. Observe the interruption of the major collateral arterial channels produced by the previous transection procedure at the level of the graft.

strates an intact and patent graft in this same animal sacrificed when healed four months after the dehiscence. A photograph of this graft appears in Fig 2.

There was little difference in the early and later results whether fresh autogenous, fresh homografts or preserved homografts were employed. A similar incidence of secondary graft failure occurred with all three types of grafts.

namely, 30 per cent, 23 per cent, and 24 per cent for fresh autografts, fresh homografts and preserved homografts respectively. The three primary graft failures with thrombosis were represented by one case in each variety of graft. There was no evidence in the course of these experiments that the preserved graft is any more susceptible than the fresh graft to the stress and infection encountered with wound complications. The ready availability of the preserved grafts of several sizes from the artery bank constituted a definite convenience for this work.

Late Function. The most significant differences in late function in those dogs surviving a sufficient time for evaluation were apparent between Group I and II animals. Dogs subjected to only one to six hours of ischemia had partial use of their legs after one or two weeks and in six weeks they had all

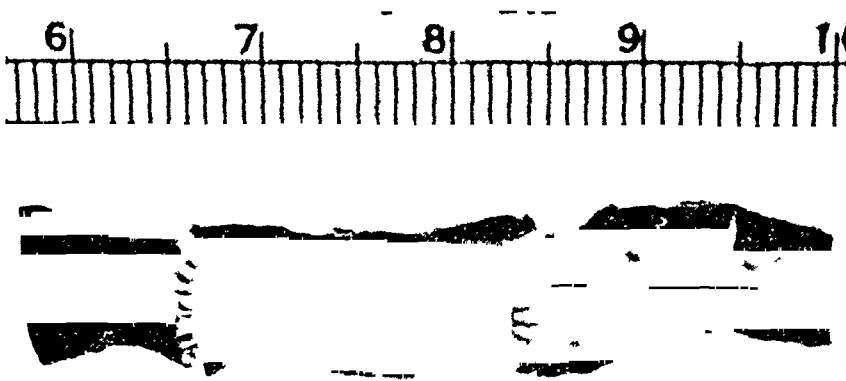


FIG 2—Photograph of the arterial graft shown in Fig 1 after fixation. There is no thrombosis or erosion of the intima in this specimen.

regained nearly normal function. There was only one animal in Group I that had more than a slight weakness or slight limitation of motion, and this dog had had a postoperative abscess of the thigh which had to be drained.

When ischemia was continued for 12 or more hours, the return of function was always delayed and incomplete with limitation of motion and loss of strength as a constant finding. Response to stimulation by pin prick of the skin of the restored leg was present in these animals. The growth of hair continued in those with more prolonged ischemia at reduced rates. All had some muscular atrophy. Contractures were present in the muscles of all the late restored legs of these dogs. In a few of Groups II and III dogs, the contractures were only slight. The majority, however, had a moderate degree of contracture. In two of the animals having ischemia for 18 and 24 hours respectively, the contractures were virtually complete, producing extremities fixed in full extension. Ambulation has been good in both of these animals on a "peg leg" and the function has been surprising. The picture which these two dogs with advanced muscular contracture present is essentially similar in certain respects to that seen in the late result of Volkmann's ischemic contracture in the human subject.

DISCUSSION

The data from these experiments, projected into terms of arterial injuries in human subjects, lend support of the view that reparative surgical treatment with early anastomosis of severed major arteries of the extremity should be practiced whenever possible. The salvage of 50 per cent of limbs ischemic for 12 to 18 hours and of 20 per cent of those ischemic for more than 24 hours in the experimental animal offers decided encouragement for the recovery of human extremities with severe vascular injuries when treatment has been delayed beyond the accepted optimum time of six to eight hours. While none of the legs in the animal preparation used in these experiments escaped gangrene when the femoral artery was ligated, it has been surmised that some collateral circulation is partially intact and sufficient to prevent gangrene in approximately 30 per cent of instances when femoral or popliteal vessels have been ligated in human leg injuries in warfare. Seldom is a complete transection of the soft tissues of the leg seen in civil injuries which is a great advantage in extending the possible limits of the "time lag."

The modifying factor of the clean wound technic used throughout these experiments has, without doubt, been an advantage in favor of these animals. On the other hand, infection and dehiscence was the prime cause of leg failure after prolonged ischemia. This was a consequence in part of ischemic necrosis of the tissues but also of the experimental limitations, which, in animals, has necessitated closure of the wound with partly devitalized tissues and bacteria buried in closed spaces. In the human subject an open wound technic is possible and desirable in the contaminated wounds and much of the infection we encountered might be avoided, and secondary hemorrhage from the anastomosis in failures reduced. The experience in the last war with wound infection was surprising.

Homograft arteries have survived sufficiently long in our dogs to pass the critical period before collateral circulation becomes effective. In fact, we believe that they have a good longevity, although other investigators¹⁷ have doubted their durability. Late studies of these grafts in surviving animals are contemplated.

We believe that the arterial graft anastomosis is the best method for joining arteries of the extremities when there is loss of arterial substance, although we have no experience in human subjects. The use of banked arteries should be practical for both civilian and military hospital groups.

Survival of the leg itself with a damaged major vessel cannot be the sole desideratum, rather, the aim should be to secure a viable leg that functions as well as possible under the existing circumstances. To accomplish this it is essential that the main vascular channel be restored to function. The few long term follow-up studies of vascular casualties available indicate a sizable incidence of functional limitation in legs with femoral and popliteal injury. Even in legs with arteriovenous fistulas which are believed to have so well developed a collateral circulation that safe ligation of the femoral or popliteal vessels is

possible without resulting gangrene, the occurrence of chronic circulatory deficiency after quadruple ligation is high¹⁸ These legs are frequently susceptible to cold, claudication is often observed and sometimes trophic changes follow It is, therefore, of importance to provide a permanent means of arterial restoration in the case of vascular injuries if good results are to be expected It is difficult to compare the impaired function seen in the legs of the dogs in the present experiments with results in human subjects As a rule the acute ischemia in the injured human leg would not be expected to reach the degree seen in these animals' legs except in the unusual transection type of wound

Although severe muscular contractures were present in some of the legs of dogs in the longer ischemia periods, the possibility of this disability occurring in the human subject should not be a deterrent to efforts to salvage the leg There is no method of determining slight variations in ischemia in legs with wounds of unknown extent and variable loss of collateral vessels As long as the extremity does not show signs of gangrene or extensive tissue deterioration, attempts to restore the circulation through the damaged main vessels should be carried out Some impairment of function can be expected in certain cases However, such sequelae can be dealt with as they present at a later observation

SUMMARY

In these experiments estimations have been made in animals on the probability of the survival of legs undergoing acute ischemia for time intervals of specific duration Three time periods which extended from the onset of the ischemia to its abolition by restoring the circulation, corresponding to the clinical "time lag," were investigated Under standard conditions of injury depriving the legs of their blood supply it was found that following restoration by arterial anastomosis the survival rate for these legs were as follows (1) for periods of ischemia ranging from one to six hours, 90 per cent survival, (2) for periods of ischemia ranging from 12 to 18 hours, 50 per cent, and (3) for periods of 24 hours or over, 20 per cent

Arterial grafts of three sorts were used with equal success These were fresh autografts, fresh homografts and preserved homografts Intravascular thrombosis in the grafts seldom occurred primarily Failure of these grafts from thrombosis or hemorrhage was secondary to infection and wound dehiscence in all but three of 23 failures of legs to survive The incidence of secondary failures were related to the period of ischemia Anticoagulants were not used in these experiments

Ischemia for a period beyond 12 hours in animals whose leg survived resulted in a variable degree of disability of the limb which was principally the consequence of contracture and atrophy

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CLINICAL EVALUATION OF TWO TESTS FOR INCIPIENT THROMBOSIS*

PROTHROMBIN ACTIVITY AND FIBRINOGEN B OF LYONS

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THE WELL-KNOWN CLINICAL SIGNS of postoperative venous thrombosis are tenderness in the lower extremity and evidence that embolism to the lung has taken place. The latter may mean a fatal issue, the former indicates that some type of radical treatment to prevent the latter should be instituted. This treatment is, of course, anticoagulant therapy or femoral vein ligation. Neither course of action gives 100 per cent protection. Obviously what is needed is a practical test which will warn of the imminence of thrombosis or will indicate its presence in the very early stages. Some tests which have been proposed are the clotting index of Bancroft and Stanley-Brown,¹ daily determinations of the coagulation time (Bergquist²), the heparin tolerance test of de Takats and Gilbert,³ the heparin titration method of Waugh and Ruddick,⁴ decelerated coagulation time determinations (Kadish⁵), prothrombin activity of diluted plasma (Brambel and Loker,⁶ Shapiro⁷), daily prothrombin time determinations (Sandrock and Mahoney⁸) and tests for fibrinogen B of Lyons.⁹

This communication presents our experience with the last two tests. No attempt will be made to explain why the others have not been adopted in clinical practice, except to state that in addition to being apparently non-specific, most of them are time-consuming and therefore impractical to carry out as screening procedures.

Sandrock and Mahoney⁸ studied the prothrombin levels of 382 patients during the postoperative period and concluded that the findings were of value in determining which patients should receive prophylactic measures against thrombosis. Their results indicated that the stage is set for postoperative thrombosis on the second or third postoperative days, and that this tendency to thrombosis can be detected by an increased prothrombin activity of the whole plasma.

We have carried out prothrombin activity studies on 283 surgical patients. Usually, the patients were chosen for study because of the presence of factors predisposing to thrombotic complications. The composition of the group with regard to the types of operations is given in Table I. Many were in the older age group, and not a few had had a previous history of thrombo-embolism. Specific treatment, if any, was not begun until the commonly accepted clinical signs appeared. As a rule, there were nine prothrombin determinations on each patient, the day before operation, the afternoon of the operation, and daily for seven days thereafter. The one-stage prothrombin method of Quick¹⁰

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was used. A commercial brand of thromboplastin (Difco) gave a normal prothrombin time of 13 to 15 seconds. In tabulating the results, the test was considered to be positive if the prothrombin activity reached 100 per cent or above on the second or third postoperative days. The cases have been divided into two groups, namely, those with no clinical evidence of thrombosis, and

TABLE I—*Operations on the Group Studied by Prothrombin and Fibrinogen B Tests*

Operation	Cases
Cholecystectomy	68
Hysterectomy	63
Gastrectomy	27
Colon operations	25
Hernia repair	18
Prostatectomy	15
Fractures	13
Leg amputation	8
Splenectomy	7
Nephrectomy	5
Miscellaneous	46
Total	295

those who were believed to have developed such a complication (Table II). In 258 patients with negative symptoms, there were 121 false positive tests. Furthermore, in more than half of the 25 cases in whom there was definite or suspicious evidence of thrombosis, there was a false negative prothrombin test.

The finding of clinical evidence of thrombosis in 25 of 283 patients (8.1 per cent) demands an explanation. It has already been mentioned that the group was weighted to some extent with regard to predisposing factors. The

TABLE II—*Correlation between Clinical Signs and Prothrombin Activity*

		Cases
Signs negative—258 cases	{ Test negative	137
	{ Test positive	121
Signs positive—25 cases	{ Test negative	15
	{ Test positive	10

clinical observers were undoubtedly "thrombosis conscious" and some questionable cases may have been included. The complications were as follows: leg thrombosis, 15 cases; pulmonary infarction, with and without antecedent clinical phlebothrombosis, 13 cases; coronary thrombosis, one case. There were four autopsies in the series, three showed thrombosis which had not been suspected clinically. There was one death due to thrombo-embolism.

Case 1—M. M., a 68-year-old woman, had a cholecystectomy for cholelithiasis. Her postoperative prothrombin activity indicated a positive test, since it was 100 per cent on the second and third postoperative days. On the 17th day, she had a pulmonary infarct. She was treated with heparin, but developed a lung abscess in the infarcted area and pyelonephritis, and expired on the 25th day from uremia. It might be argued that the

should have received anticoagulants because of her positive test, but to be consistent we would have to have treated 121 other positive cases who never showed any clinical evidence of intravascular clotting

The following case summary is an example of the group of cases which showed clinical thrombosis without warning from the prothrombin determinations

Case 2—M H, a 62-year-old man, had a partial gastric resection on Nov 12, 1948. The prothrombin levels on the first, second, third and fourth postoperative days were 90 per cent, 89 per cent, 80 per cent and 56 per cent respectively. On the fourth day, tenderness was noted in the left calf, and there was a positive Homans' sign. Shortly afterward he had pain in the chest. Heparin was begun, and thereafter his convalescence was uneventful.

On the basis of the experience outlined above, we concluded that in our hands the test for prothrombin activity was not specific enough to be of value in picking out patients in the prethrombotic state.

FIBRINOGEN B OF LYONS

Our interest in "fibrinogen B" was stimulated by the appearance of an article by Cummine and Lyons⁹ in *The British Journal of Surgery*. Lyons¹¹ had previously published the results of some of his blood coagulation experiments and he concluded

that the clotting of fibrinogen by thrombin occurs in at least two stages, the initial step is the liberating of blocked thiol groups in fibrinogen brought about by one component of thrombin, the second, an oxidation, probably by a naphthoquinone complex in the thrombin converting protein-SH to protein -S-S- protein (fibrin). The native fibrinogen was designated by the letter A. After it was acted upon by the component A of thrombin (not to be confused with component A of prothrombin of Quick¹²), it became fibrinogen B and was that much closer to becoming fibrin, or the true clot. Lyons' conception of the blood clotting mechanism is summarized in Fig 1. In the first paper, Lyons used 2-methyl-1,4-naphthoquinone to cause the fibrinogen B to gel. The test described in the second paper is as follows. A reagent is prepared by dissolving 2 Gm of β -naphthol in 100 cc of 50 per cent alcohol and then exposing this solution to oxygen until it turns brown. Four and one-half cc of blood is mixed with 0.5 cc of 1 per cent sodium oxalate. This is centrifuged and 1 cc of the plasma is pipetted off into a 13 x 100 mm tube. To this is added 5 drops of the reagent. After shaking, the mixture is allowed to stand for 10 minutes, when it is examined for clot formation. A negative and a positive test may be seen in Fig 2.

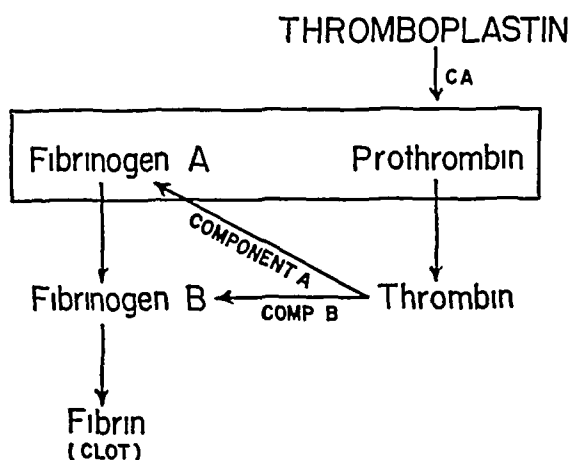


FIG 1—Schema of normal blood coagulation, according to Cummine and Lyons. *Brit J Surg*, 35: 337, 1948.

Lyons states that both "profibrin" and fibrinogen B form a gel with the β -naphthol, but the profibrin appears only when the Fibrinogen B content is very high, and since both substances are significant clinically from the viewpoint of thrombosis, it is desirable to use the test which demonstrates both



FIG 2—Lyons' test for fibrinogen B. An alcoholic solution of β -naphthol has been added to the plasmas of two patients. After a 10-minute interval the tubes have been tipped to an almost horizontal position. The test on the left is negative, that on the right, positive.

substances. He states that if it is necessary to determine fibrinogen B alone, a 5 per cent aqueous solution of hydroquinone-quinhydrone should be used and the plasma examined for clot formation in 30 minutes. It should be clearly understood that we have made no attempt to investigate the validity of Lyons' test of blood coagulation or to check the chemical reactions involved.

Cummie⁹ used Lyons' test on a number of surgical patients in the Royal

Prince Alfred Hospital in Sydney. He concluded that it is possible, by the use of the coagulation graph (Bergquist) and the fibrinogen B estimations, to subdivide patients who are to undergo surgical procedures into four groups (1) Those patients in whom free fibrinogen B does not occur in the plasma and the coagulation graph is of normal type (*i.e.*, clotting time above three minutes by the capillary tube method). Intravascular thrombosis does not develop in these cases. (2) Fibrinogen B may be found in the plasma either persistently or intermittently, but the coagulation graph is normal. In the absence of previous thrombosis or venous stasis, thrombosis does not develop in these cases. (3) Fibrinogen B occurs in the plasma and the coagulation time remains persistently low, in the order of three to four minutes. Intravascular thrombosis appears to be inevitable. (4) No fibrinogen B appears in the plasma but the coagulation graph is low. This has been observed after an intravascular thrombosis has occurred. (Has the fibrinogen B been used up?)

TABLE III—*Correlation between Clinical Signs and Fibrinogen B Tests*

		Cases
Signs negative—109 cases	{ Test negative	77
	{ Test positive	32
Signs positive—18 cases	{ Test negative	4
	{ Test positive	14

We carried out fibrinogen B tests on 127 postoperative patients. One hundred and sixteen of these also had the tests for prothrombin activity described earlier in the paper. It was therefore possible to observe the effectiveness of the two tests on the same patients in many instances.

The results are summarized in Table III. A little less than a third of the patients in whom no signs of thrombosis developed gave a false positive test. Eighteen patients out of 127 (14.2 per cent) were thought to have thrombosis clinically. In 14 of these, the fibrinogen B test was positive, leaving only four false negatives.

It should be pointed out again that the 18 instances of postoperative thrombosis did not develop in a general cross section of surgical patients, but in a group of thrombosis-prone patients.

Case 3—B. F., a 35-year-old male. A spleno-renal anastomosis was carried out following splenectomy and nephrectomy for bleeding esophageal varices. The patient had further fatal hemorrhage in spite of the operation, and the autopsy showed thrombosis in the splenic vein behind the pancreas and remote from the anastomosis. The fibrinogen B test had been positive on the day of operation, and each day until the patient died. The prothrombin activity on the second day was 70 per cent.

Reference should be made to Case 2 above. The postoperative prothrombin activity was consistently below normal, but the fibrinogen B test was positive on the second, third and fourth days before clinical thrombosis was detected.

On the other hand, there were several times when the test failed to warn of impending thrombosis, as in the following example

Case 5—G K was a 44-year-old woman on whom hysterectomy was carried out. On the first postoperative day the fibrinogen B was negative. On the second day the prothrombin activity was 100 per cent (positive test). On the third day the fibrinogen B was again negative, but on this day tenderness developed in the left calf, and it was deemed urgent to begin heparin therapy.

TABLE IV—*Results of Fibrinogen B Tests in Prothrombin-tested Patients with Clinical Signs*

	Fibrinogen B Test	Cases
Signs positive, prothrombin test negative—15 cases	{ Negative	1
	{ Positive	7
	{ No test	7
Signs positive prothrombin test positive—10 cases	{ Negative	3
	{ Positive	4
	{ No test	3

It is of interest to see how often the fibrinogen B test was right when the prothrombin test was wrong, and vice versa. In Table IV, the 25 "Signs Positive" cases from the lower half of Table II have been tabulated with respect to what the fibrinogen B test showed if it was done. It is striking that of 15 cases with positive signs and negative prothrombin tests there was only one which showed a false negative fibrinogen B test.

Similarly, Table V tabulates how the prothrombin test reacted in the 18 patients with positive signs who had fibrinogen B tests. There were seven false negatives in a group of 14 cases with positive signs and positive fibrinogen B tests.

TABLE V—*Results of Prothrombin Tests in Fibrinogen B-tested Patients with Clinical Signs*

	Prothrombin Test	Cases
Signs positive, fibrinogen B negative—4 cases	{ Negative	1
	{ Positive	3
Signs positive fibrinogen B positive—14 cases	{ Negative	7
	{ Positive	4
	{ No test	3

As an additional study, single tests were done on 83 ambulatory individuals in the out-patient department. Only two of these showed a positive test.

CONCLUSIONS

We were unable to confirm the finding of Sandrock and Mahoney that daily determinations of the prothrombin activity of the plasma is a valuable screening test to predict thrombotic complications in postoperative patients. A somewhat more specific test is that described by Lyons which involves the

addition of an alcoholic solution of β -naphthol to plasma Lyons believes that the resulting gel formation is due to what he calls fibrinogen B, and that it indicates a thrombotic tendency Further clinical and chemical investigations of this reaction are in order

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DISCUSSION—DR EARLE B MAHONEY, Rochester, N Y We have been very interested in hearing of Dr McClure's results, and are a little disappointed that he has not been able to confirm our feeling in respect to prothrombin activity

I would like to bring you up-to-date on our experiences, as we still feel that the test has some value, in predicting postoperative thrombosis

(Slide) This slide was presented last year The solid line below in the graph indicates the average prothrombin activity level in patients who do not develop thrombosis The black dots to the right of the middle line show patients who did develop thrombosis and who had an increased prothrombin activity on their third or fourth postoperative day

(Slide) This was a summary of our cases up to the time of this meeting last year We had investigated 309 cases at that time Of that group there had been 42 per cent who had developed thrombosis Those who had developed thrombosis had a 100 per cent increase in the activity of their prothrombin, in other words all 42 per cent of these patients had increased prothrombin activity on their second, third or fourth postoperative days

(Slide) This shows our results during the past year, in the series of patients that we have studied We have followed 405 patients, which brings our total to the neighborhood of 800 Of these, there was no hyperprothrombinemia in 365 patients, there was an increased prothrombin activity in forty of the 405

(Slide) Breaking down this group who had hyperprothrombinemia, there were 19 patients who did not have thrombosis. These 19 patients were primarily young individuals who were mobilized immediately after operation, also, this group comprised an interesting series of patients, those who have been operated on under tourniquets.

We have found a rather high incidence of hyperprothrombinemia in patients who have had tourniquets used during the operation, even though no thrombosis clinically develops postoperatively.

There were nine patients of the total of 40 who were given prophylactic dicumarol because of hyperprothrombinemia. Twelve patients did have hyperprothrombinemia who did not receive any dicumarol and who did develop definite venous thrombosis postoperatively.

In these 415 patients, as with the preceding 309, we have not seen a patient develop thrombosis who has not had a preceding hyperprothrombinemia.

In other words, our present evaluation of the test is that by this means we can select from all surgical patients a group who should be watched carefully and who should perhaps be given dicumarol therapy.

I would like to call attention to the fact that the determination of prothrombin activity on plasma is not specific for prothrombin, but we are merely testing the rapidity of plasma clot formation and the presence of calcium and thromboplastin. I believe last year we mentioned that because this test is positive in the whole plasma rather than in the dilute plasma, we felt we perhaps were measuring something other than prothrombin which was a precursor of this thrombosis.

We are delighted to hear of Dr. Lam's and Dr. McClure's work, because it is quite possible that this material which we are looking for may be fibrinogen B. There are many other factors which still remain to be investigated, and I am extremely interested in Dr. Lam's results.

MAJOR EDWIN J. PULASKI, San Antonio, Texas: At Brooke General Hospital my associate, Lieutenant Arthur Voorhees, and I have been studying for the past year the fibrinogen B test, and a few remarks concerning our findings at this time might be pertinent to the discussion.

First, we find that this test is considerably labile, and that there is a marked temperature effect; this means the results will be different with the plasma if the test is performed at 6° C room temperature or 37° C. This is not stressed in the paper of Cummine and Lyons (Brit J Surg 35 337, 1948). The highest percentage of positive tests is obtained when the experiment is carried out at 6° C.

Secondly, this test is alleged to be an indication of thrombosis which has not yet occurred but which is incipient. We find that in patients who have already developed signs of thrombosis the test may or may not be positive, but that the positive test will disappear within 24 to 36 hours after signs of thrombosis have occurred, then remain negative.

Thirdly, and perhaps most importantly, we have found that this is not a specific test for thrombosis, but it would appear to be positive, at least inconstantly so, in all cases of spreading infection. Also, this test does appear to be positive in all cases where there is considerable tissue necrosis, such as in thermal burns.

Inasmuch as it would not appear to be specific for incipient thrombosis, the fibrinogen B test of Cummine and Lyons, in our experience, does not promise to become a valuable adjunct to the clinical diagnosis of thrombosis at this stage of development of the test.

DR. CONRAD R. LAM, Detroit: I have very little to add. I appreciate Dr. Mahoney's remarks, and I think our two series could come a little closer together if we were better agreed on what constitutes hyperprothrombinemia.

If you will remember his first slide, there were a number of black dots indicating hyperprothrombinemia just above the 100 per cent line, and they were put up there because the person holding the stop watch clicked it just about a tenth of a second sooner. Our technicians do not claim to have that good a reaction time, and the surgical residents who try to perform this test usually record the prothrombin time in terms of half a second rather than trying to get any closer. Our laboratory reports nothing higher than 100 per cent, although they have obliged us by reporting the time in seconds also.

I am glad to hear that someone else is trying to see if there is anything to the fibrinogen B test, and Major Pulaski's observations are very interesting. Dr. Lyons, in his article, stresses that the test is positive in cases of infection, and a number of other conditions. Dr. Margulis, who did most of these tests, reported to me that the very vigorous centrifuging of blood to get the plasma, instead of letting the cells settle out, tends to produce a false positive test.

PHYSIOLOGIC STUDIES IN CASES OF STRICTURE OF THE COMMON BILE DUCT*

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MY INTEREST in the treatment of strictures of the common and hepatic bile ducts dates back to 1924. From that time until January 1, 1949, I have operated on 186 patients for stricture of the extrahepatic ducts. I have divided these cases into two groups: (1) a series of 98 cases in which operations were performed from 1924 through 1939 (Table I), and (2) a series of 88 cases in which 113 operations were done from 1940 through 1948 (Table II). Lewis, Friedell and I reported on the first group in three papers in 1940 and 1942^{1, 2}. In the study of this second group I have had the help of my first assistants, Drs. Spencer Phillips³ and John Cameron, and Dr. Joseph Berkson of the Section on Biometry and Medical Statistics of the Mayo Clinic.

In the first series, the hospital mortality rate was 10.2 per cent and in the second series it was 3.4 per cent (or 2.6 per cent on the basis of 113 procedures). This reduction in mortality rate, I think, can be directly attributed to a better understanding of the pathologic physiology of the liver in cases of biliary obstruction and the institution of adequate methods of treatment before, during and subsequent to operation in order to compensate for the disturbances, rather than to any particular improvement in the technic of the surgical procedure. There are, perhaps, a few exceptions to this statement, the first is that I have been able to find remnants of extrahepatic ducts above the stricture more frequently in the second series of cases than in the first, because I have searched more diligently for them, even incising the parenchyma of the liver. The same is true of the identification of the lower end of the common duct. For this reason the proportion of duct-to-duct anastomoses to those of a duct to the duodenum has increased. In 11 of the 27 cases of stricture in which I performed operations in 1948, choledochocolicostomy was performed, in 13 hepaticoduodenostomy, in 1 choledochoduodenostomy and in 2 hepaticostomy. The incidence of duct-to-duct anastomosis in 1948 was 40 per cent in contrast to 11.2 per cent in the cases from 1924 through 1939 and 18.6 per cent in the cases from 1940 through 1947. Assuming that an anastomosis of the end of the duct to the intestine is possible, the problem that will concern the surgeon is whether to anastomose the stump of the duct to an opening made in the duodenum or to one of the loops of the jejunum. With the latter procedure the duct is anastomosed to the jejunum either with an enteroanastomosis or with a Roux-Y type of anastomosis, as recommended by Allen⁴ and Cole⁵.

Before considering this question, let me return briefly to a discussion of the pathologicophysiological changes associated with biliary obstruction and the

* Read before the American Surgical Association, St. Louis, Mo., April 21, 1949.

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preoperative and postoperative methods directed to their treatment. Although I would like to discuss tests of liver function, time does not permit more than saying that studies of the response of the prothrombin time of the blood to vitamin K, the amount of serum globulin and its relation to the serum albumin have proved in our experience, the most practical indicators of the degree of

TABLE I—Results According to Operation Structure of Common and Hepatic Ducts, 1924 Through 1939

Operation	Cases	Well When Last Heard From		Recurrence of Biliary Obstruction		Hospital Deaths		Subsequent Deaths	
		No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
Common duct to duodenum	34	28	82.4	2	5.9	1	2.9	3	8.8
Hepatic duct to duodenum	31	13	41.9	8	25.8	2	6.5	8	25.8
Duct to duct	11	6	54.5	2	18.2	1	9.1	2	18.2
Hepaticostomy	9	2	22.2	2	22.2	3	33.4	2	22.2
Transplantation of external biliary fistula	9	2	22.2	4	44.5	1	11.1	2	22.2
Other	4	1	25			2	50.0	1	25
Total	98	52	53.0	18	18.4	10	10.2	18	18.4

liver damage associated with a stricture. If the blood contains globulin in excess, and an elevated prothrombin time does not promptly return to normal after the administration of vitamin K, more than the average amount of injury to the liver parenchyma is likely to have occurred. The frequency with which intrahepatic biliary block may simulate extrahepatic block must be remembered in all cases in which jaundice occurs, and this is especially important when

TABLE II—Types of Operation for Structure of Biliary Ducts 1924 Through 1948

Type of Operation	1924-1939		1940-1947		1948	
	No *	Per Cent	No †	Per Cent	No †	Per Cent
Duct to duct	11	11.2	16	18.6	11	40.7
Hepatic duct to duodenum	31	31.6	39	45.4	13	48.2
Common duct to duodenum	34	34.7	10	11.6	1	3.7
Hepaticostomy	9	9.2	11	12.8	2	7.4
Other	13	13.3	10	11.6		
Total	98	100	86	100	27	100
* Number of patients						
† Number of operations						

jaundiced patients have had previous operations on the biliary tract. The concentration of blood lipids are increased in the presence of obstructive jaundice and decreased in the presence of severe hepatic injury. When hepatic damage has occurred, the concentration of gamma globulin in the serum is increased and that of serum albumin is decreased. These findings are extremely reliable and the tests are not difficult to perform.

At the Mayo Clinic all patients who have jaundice are hospitalized for at

least three days prior to surgical intervention. In this period, study of hepatic function is made and the patient is prepared for operation by administration of vitamin K or some other similarly acting substance and a forced increase in the intake of carbohydrate and protein. In addition, parenteral injections that are necessary are given. If the prothrombin time is elevated and is not reduced after administration of vitamin K, blood transfusions are employed before operation. I cannot remember a single case of stricture of the bile ducts in which I have refused to operate when recurrence of the stricture has taken place, regardless of how deeply jaundiced the patient was or how many previous operations had been performed for correction of the biliary stricture. I mention this not to emphasize particularly the success that may be obtained by a properly performed procedure, even after as many as three to five previous unsuccessful attempts at repair, but to illustrate that reduction of the hospital mortality rate in my two series of cases can be attributed mainly to recent preoperative and postoperative study of the patient and his liver, institution of treatment indicated by this study both before and after operation, and the performance of a proper surgical procedure which completely relieves the biliary obstruction.

In recent years the question of effect of regurgitation of food and of gastric, duodenal and pancreatic secretions into the biliary ducts has been a matter of considerable speculation and some study. I have followed carefully all of the patients on whom I have operated since January, 1924, that is, for 25 years. *In my experience now with approximately 118 cases in which the common or hepatic duct has been anastomosed to the duodenum (in 65 for more than ten years),* I have been unable to prove that any reflux from the duodenum was productive of either asymptomatic or symptomatic infection of the liver. A similar observation was made on animals by Soupault in France.⁶ Moreover, in my patients, when fever or jaundice with and without pain has led to speculation on this possibility, reoperation has always shown recurrence of the obstruction, usually of a considerable degree, at the site of the previously performed hepaticoduodenostomy, choledochoduodenostomy or choledochocolicostomy.

Of the 98 patients operated on from 1924 through 1939, 34 had sufficient duct above the stricture to anastomose it accurately to the duodenum. When these cases were studied by Lewis, Friedell and me in 1940, 82.4 per cent of these 34 patients were living and well. This group of cases, as well as the entire series, is under intensive investigation to determine the percentage in which obstruction has been cured for ten years or more.

Roentgenographic studies of the duodenum and anastomosed duct after the oral ingestion of barium have shown both air and barium in the ducts, to a greater or less degree in the cases in which the anastomosis was not obstructed. On the other hand I have found recurring obstruction, when, because of pain or fever with or without jaundice, I have reoperated on patients who have had a previous operation or operations for stricture and who have not had this reflux of barium or air from the duodenum into the common

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or hepatic ducts. In a few cases even though air and a small amount of barium were noted in the ducts, attacks of pain with or without fever, and mild transient jaundice, have occurred. At operation, contraction of the duct, sometimes to a few millimeters in diameter at the site of the anastomosis, has been found in these cases.

I presented two examples of this before the members of the Chicago Surgical Society at their meeting in Rochester, Minnesota, on January 19, 1949. I shall only mention one of these cases here, however. In this case I performed hepaticoduodenostomy 11 years ago at which time only a fringe of hepatic duct was found to anastomose to the duodenum. The patient was well for ten years and then had attacks of biliary colic with questionable slight jaundice of skin and sclera. At operation, contraction of the duct at the site

TABLE III—*Results According to Operation for Stricture of Common and Hepatic Ducts 1940 Through 1947*

Operation	Total Cases	Hospital Deaths		Cases Traced*	Well When Last Heard From		Recurrence of Biliary Obstruction		Died Elsewhere	
		No	Per Cent		No	Per Cent†	No	Per Cent†	No	Per Cent†
Common duct to duodenum	9	0	0	7	5	71.4	1	14.3	1	14.3
Hepatic duct to duodenum	32	1	3.1	25	16	64.0	3	12.0	6	24.0
Duct to duct	12	0		8	4	50.0	4	50.0	0	
Hepaticostomy	8	1	12.5	6	0		5	83.3	1	16.7
Others	4	0		4	4	100.0	0		0	
Total	65	2	3.0	50	29	58.0	13	26.0	8	16.0

* Patients operated on too recently for judgment of results and cases in which follow-up information was not available at this date are omitted.

† Per cent of cases traced.

of the anastomosis had reduced the lumen to a few millimeters in diameter. Plastic enlargement of the stoma was carried out and the patient has been well since.

The operation, anastomosis of the end of the biliary duct to the duodenum, when the lower segment of the duct cannot be found, is a relatively simple operation compared to that required to anastomose the duct to the jejunum. The simplicity of choledochoduodenostomy or hepaticoduodenostomy makes these procedures my operations of choice since many of the patients on whom I operate have had at least one unsuccessful attempt at repair (Table III). In point of fact, of the 27 patients I operated on during 1948, one had five previous procedures on the biliary tract, four had four, six had three, nine had two, and seven had one operation (Tables IV and V).

I have seen identical symptoms, that is pain, chills, fever or jaundice alone or in various combinations, not only in cases of contracture at the site of the biliary-duodenal anastomosis but also in cases of contracture of anastomosis between the reconstructed ends of the common duct. This brings up the question as to whether, in order to preserve the mechanism of the sphincter of Oddi at the lower end of the common duct and to prevent reflux of duodenal con-

tents into the biliary tree, it is worth while to subject the patient to diligent search for the end of the common duct below the stricture. It is debatable whether stricture does not recur more frequently when the continuity of the duct itself is re-established than when the proximal end of the duct is anastomosed to the duodenum. This problem is being investigated at present. Of

TABLE IV—*Analysis of Procedures (Operations) Author's Series, 1948*

Operation	Cases	Prosthesis Used		
		T Tube	Polythene Tube	Catheter
Duct to duct	11	7		4 (McArthur)
Hepatic duct to duodenum	13	7	6	
Common duct to duodenum	1		1	
External hepaticostomy	2			2
Total	27	14	7	6

course the type of end-to-end anastomosis employed will make a difference in the number of recurrences when ductal continuity has been re-established. In all circular anastomoses, concentric contraction tends to occur whereas after an angulated anastomosis, that is, in one in which triangular shaped ends are sutured, concentric contraction does not occur. Unfortunately, as a rule, insufficient duct ends are present to perform an angulated anastomosis. Therefore, the problem usually is to determine what type of indwelling casting or

TABLE V—*Relation of Number of Previous Operations to Procedure Author's Series, 1948*

Procedure	Cases	Previous Operations				
		1	2	3	4	5
Duct to duct	11	6	3	1	1	
Hepatic duct to duodenum	13	1	3	5	3	1
Common duct to duodenum	1		1			
External hepaticostomy	2		2			
Total	27*	7	9	6	4	1

* 6 previous operations by author

tubing will prevent contracture of the circular type of anastomosis and how long it should remain in place to accomplish this purpose. McIndoe⁷ has stated that a period of three months is necessary to prevent contracture of tubular grafts of skin. In my opinion three months is the minimal period that splinting tubes should be kept within the common duct and from six to twelve months is probably better. Any tube used to splint the ductal anastomosis will sooner or later have its lumen occluded by bile pigment and salts and will obstruct the duct unless removed. I have removed Vitallium and rubber tubes from the common duct which were filled and encrusted with bile pigment or salts and which could not pass the sphincter of Oddi. A rubber catheter, most of which extends beyond the sphincter of Oddi into the duodenum, has seemed the best type of splint to me. It can be held in place for as long as desired by a silk thread passed through it and attached to the surface of the skin as

recommended by McArthur. When the silk suture is removed, intestinal peristalsis will pull the catheter into the duodenum and it will pass through the intestinal tract without stopping or obstructing. Tubes of rubber, Vitalium, or polythene can be used in a choledochoduodenostomy or hepaticoduodenostomy. Bile, however, accumulates in the lumina and about the exterior of rubber and Vitalium tubes. This happens less frequently when polythene tubes are used. These tubes will pass spontaneously into the duodenum in a few weeks unless fixed in position with the long silk suture used to fix a catheter.

In the surgical procedure, I employ an upper right rectus incision. I have been able to see no clinical indications that a general anesthetic or combined nitrous oxide, ethylene, oxygen and ether is disturbing to liver function and have preferred this type of anesthesia. I keep the dissection close to the under surface of the liver; I extend it as far laterally as possible and expose Morrison's pouch. From this starting point the dissection is carried mesially until the structures of the hepaticoduodenal ligament are reached. It is then carried from the mesial part of the right lobe of the liver at a deep level to the hepaticoduodenal ligament in order to expose the hepatic artery. After exposure of the hepatic artery in the hepaticoduodenal ligament, it is nearly always possible, by upward traction on the under surface of the liver and by dissecting along the hepaticoduodenal ligament into the hilus of the liver, to find the proximal stump of the common or hepatic duct of sufficient length to use in an anastomosis either to the lower part of the duct or to the duodenum. This I was able to do in 25 of the 27 cases in which operations for stricture of the biliary ducts were performed in 1948.

SUMMARY

A study of the 186 cases of stricture of the common and hepatic bile ducts in which operations were performed, has given evidence of the beneficial effects of studies of liver function and preoperative and postoperative treatment directed toward compensating for the disturbances resulting from the biliary obstruction. Prevention of bleeding has been accomplished by the administration of vitamin K and blood. As a result, the syndrome of hepatorenal insufficiency does not occur. More diligent search for both ends of the duct beyond the stricture has been productive of a greater percentage of cases in which anastomosis of the duct to the duct or the duct to the duodenum could be accomplished. As an indication of the benefits of this routine the mortality rate of 10 per cent in the 98 cases in which operation was performed from 1924 to 1939 inclusive has been reduced to 3.4 per cent in the 88 cases in which operation was performed from 1940 to 1948 inclusive. If the mortality rate in the last group is figured on the basis of operative procedures, since reoperations were performed for recurrence of the stricture in some cases, it is only 2.6 per cent.

During these years evidence accumulated indicates that after a biliary-duodenal anastomosis, reflux of food (barium or air) into the common and

hepatic ducts is not responsible for pain, fever or jaundice but that these symptoms are the result of recurring obstruction of varying degree at the site of the previously made anastomosis. This is important because of the simplicity and ease of these operations in comparison to the operation needed to anastomose the duct to the jejunum, especially if the Roux-Y principle of jejunal anastomosis is used.

Studies are under way to determine whether results of anastomosing the ends of the duct are as good, better or worse than those of anastomosing the proximal end of the duct to the duodenum. Involved in this problem is the fact that concentric contraction occurs at the site of most circular or tubular ductal anastomoses to a greater or less degree unless prevented by a tubular prosthesis until the usual period of such contracture has passed. Whether this applies to a greater degree in anastomosis of duct to intestine remains to be determined. Hence the question arises whether in order to preserve the function of the sphincter of Oddi an operation should be performed which may be followed by a higher incidence of recurring obstruction at the anastomosis than follows choledochoduodenostomy.

To prevent contracture of a circular biliary ductal anastomosis, a rubber catheter extending from the hepatic duct into the duodenum may be used as a splint. The catheter which will be pulled into the duodenum by peristalsis can be maintained in position by a silk suture passing through it and brought out to the skin where it is anchored to a button as advised by McArthur. Other short tubes, even of Vitallium, placed within the duct will have their lumina plugged and obstructed by bile and bile will accumulate about them. This foreign body will obstruct the common duct unless removed, for they will not pass through the sphincter of Oddi. Hence they should not be used. Prostheses of any type used to prevent contracture in anastomosis of duct to intestine will likewise become obstructive agents if they remain in place too long. Fortunately this practically never occurs because they will pass into the intestine within a few weeks unless prevented from doing so by fixation with a silk suture brought to the exterior.

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INTRAHEPATIC CHOLANGIOJEJUNOSTOMY FOR BILIARY OBSTRUCTION — FURTHER STUDIES*

REPORT OF FOUR CASES

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ANASTOMOSIS OF one of the intrahepatic biliary ducts to the jejunum following a partial resection of the left lobe of the liver for certain extensive benign strictures of the extrahepatic biliary system was described in a previously published article¹. The procedure was suggested for those cases in which the usual methods of biliary reconstruction had proved inadequate. Experimental studies and a report of a case in which this method was used successfully were presented.

Three additional patients have since been treated by this procedure and it is the purpose of this paper to review our experience with the operation.

TECHNIC

A V-shaped bilateral subcostal incision extending farther to the left than to the right, used in all cases, gave satisfactory exposure. Extension of the incision to the right of the mid-line permitted mobilization of the entire left lobe of the liver. Although all patients had been subjected to at least three previous right upper abdominal operative procedures, adhesions in the left upper part of the abdomen were not numerous and mobilization of the left lobe of the liver from the diaphragm and the surrounding structures was readily accomplished. The diameter of the intrahepatic duct isolated for the anastomosis was indicated by the size of the catheter which could be passed into the duct. Case 1, No. 14 French catheter, Case 2, No. 14 French catheter, Case 3, No. 20 French catheter, Case 4, No. 18 French catheter. Smaller ducts, of course, were present, but if the incision was carried deep enough into the liver to expose a major branch of the intrahepatic biliary system, a duct of the desired caliber was found to be available in these adult patients with chronic biliary obstruction (Figs. 1 and 2).

The major intrahepatic ducts lie in the inferior or caudal half of the substance of the left hepatic lobe, at times quite near the inferior surface. As the hepatic incision was carried into the middle third of the substance of the left

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lobe, a dense fibrous cord which contains a major branch of the intrahepatic biliary system was encountered. This fibrous cord was located without undue difficulty as it is much firmer than the surrounding hepatic tissue. Before dividing this structure, additional length of the duct for anastomosis was obtained if the cord was freed distally by curetting away the surrounding hepatic tissue. Since the fibrous cord, however, contains a branch of the hepatic artery and a branch of the portal vein, it was incised with caution. Bleeding from the artery and the vein must be controlled without encroaching on the

FIG 1



FIG 2

FIG 1—Cut surface of left lobe of liver with catheter in intrahepatic duct. Roux type jejunal segment mobilized for anastomosis. Note position of duct opening immediately beneath the level of the anterior abdominal wall.

FIG 2—Anastomosis completed. Antimesenteric border of jejunum being sutured to superior surface of liver. End of catheter, which passes through the anastomosis, can be seen protruding into wall of jejunum.

lumen of the duct. For positive identification, a catheter was passed proximally into the duct and bile was aspirated before the anastomosis was begun.

A careful mucosa-to-mucosa anastomosis of the duct to the jejunum was greatly facilitated by the excellent exposure and accessibility of the end of

the duct provided by the technic. Instead of attempting to suture structures located deep in the hilar region of the liver, anastomosis of the duct in this procedure was performed just beneath the level of the anterior abdominal wall. As many as 14 interrupted 00000 silk sutures were placed about the circumference of the anastomosis for accurate approximation of the mucosal layers.

The length of one side of the wedge-shaped segment was determined by the depth of the selected duct from the anterior edge of the liver. The incision was continued in such a manner as to remove a segment of hepatic tissue so that the anastomosis might be readily performed and so that the intestine would not be acutely angulated when it was placed over the cut hepatic surface.

A rubber catheter passing from the duct into the intestine was, in the past, sutured into the anastomosis with catgut. It has been felt, however, that this is unnecessary, and that the catheter might become a source of difficulty at a subsequent time should it not be passed.

A Roux segment of defunctionalized jejunum was used in the later cases rather than the jejunal loop described in the original operation. This single limb facilitated the operative procedure and probably provided a more completely defunctionalized intestinal segment than did the jejunal loop with a proximal enteroenterostomy.

POSTOPERATIVE COURSE

A satisfactory explanation is not available for the marked rise in the serum bilirubin which occurred during the first postoperative week in three of these cases. The serum bilirubin returned to an approximately normal level within four weeks after operation in two cases but did not return to the normal range for two months in the other two cases. There was a moderate drainage of bile-colored fluid from the incision during the first few days after operation in all the cases, but such discharge stopped promptly after removal of the intraperitoneal drains. Daily elevations of temperature occurred in all the cases for at least two and a half weeks after operation.

Postoperative complications developed in two patients. A large intraperitoneal abscess, presumably resulting from a previous exploration, was inadvertently opened during the operation in Case 3. Subsequent drainage of five large intraperitoneal abscesses was required. In addition, a high intestinal fistula which developed through a former operative scar, was treated by constant suction and it closed spontaneously. Severe, unexplained bleeding into the gastrointestinal tract, with repeated passage of tarry stools during the second and third weeks after operation, occurred in Case 4. Erosion of the jejunal mucosa by the catheter in the biliary-jejunal anastomosis was suggested as the cause of this hemorrhage. Repeated transfusions were given and the bleeding stopped spontaneously. Three months after operation this patient was readmitted to the hospital deeply jaundiced and died within a few hours. At postmortem examination, the cholangiojejunal anastomosis was widely patent and was well healed. There was free communication of the right and the

TABLE I

Case No	Date Operation	Postoperative Complications	Survival	Remarks
1	4/2/1947	None	2 years	Well 22 months Recent upper abdominal abscess and external biliary fistula which healed spontaneously Severe cerebral arteriosclerosis Biliary drainage adequate at present
2	3/20/1948	Multiple intra abdominal abscesses High intestinal fistula	13 months	Prolonged, difficult postoperative course Occasional attacks of cholangitis Now well Has bile in stools Serum bilirubin slightly elevated
3		None	11½ months	Well since operation
4	9/14/1948	Unexplained hemorrhage into gastrointestinal tract	3 months	Slow recovery but jaundice cleared completely Patient well until onset of fatal attack homologous serum jaundice

left main intrahepatic ducts at the hilus of the liver The extensive destruction of the hepatic cells seen in the microscopic sections of the liver was compatible with a diagnosis of homologous serum hepatitis, and this was considered to be the cause of death (Fig 3) Evidence of a spreading cholangitis was not discovered A brief summary of the four cases is given in Table I

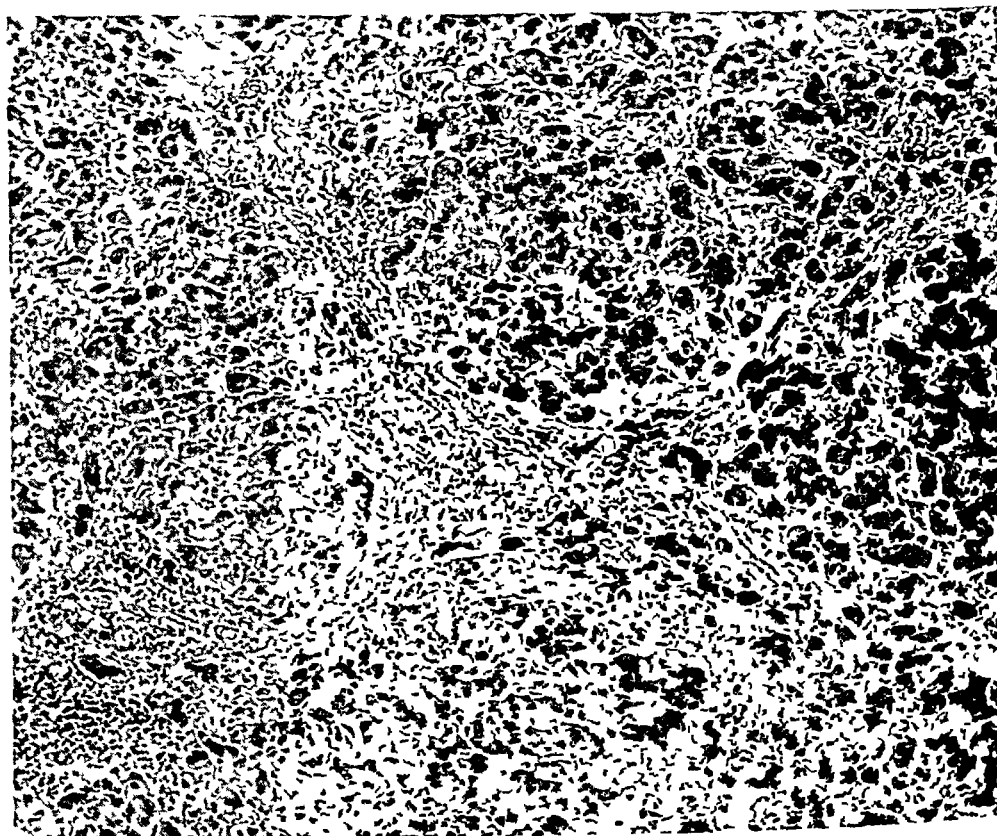


FIG 3—Photomicrograph of liver in Case 4 at the time of death, three months after operation, showing acute hepatic necrosis compatible with homologous serum jaundice

DISCUSSION

Walters and Phillips² state that 20 per cent of patients operated on for repair of stricture of the bile duct will require another operation because of the recurrence of biliary obstruction. Lahey,^{3, 4} Cattell,⁵ and others have emphasized the difficulties encountered in secondary biliary repairs, such as extensive scarring in the region of the hepatoduodenal ligament, the obliteration of landmarks, and the destruction of the proximal end of the common bile duct or of the common hepatic duct.

Numerous methods have been devised for the treatment of these difficult recurrent cases of biliary stricture, all, however, have involved reexploration of this densely scarred and distorted hepatoduodenal region in which there is the ever present danger of serious injury to the portal vein or the hepatic artery. When the upper end of the common hepatic duct is extremely short or nonexistent it is difficult to perform an accurate mucosa-to-mucosa anastomosis in this area, regardless of the method used.

Our experience with cholangiojejunostomy was encouraging in all four of the cases in which the procedure was attempted. Mobilization of the left lobe of the liver was accomplished without undue difficulty. Bleeding from the cut surface of the liver was satisfactorily controlled by the mattress sutures described in the original technic.¹ The size of the intrahepatic ducts, the thickness of their walls, and the accessibility of the ends of the ducts made it possible to perform accurate mucosa-to-mucosa anastomosis with the jejunal segment in all cases. Other surgeons^{2, 3} have successfully utilized the procedure in instances of extensive extrahepatic biliary obstruction.

It is not known what result may be expected to follow this operation if the obstruction in the biliary system extends high enough to block the communication of the left and the right main intrahepatic ducts.

However, Lahey⁴ reported successful anastomosis by Doctor Cattell of the left hepatic duct when it was impossible to find the right because of the depth of the scarred duct within the liver. Atrophy of the right lobe and enlargement of the left occurred with adequate maintenance of hepatic function. If only a portion of the intrahepatic biliary system is to be drained, our experience would suggest that partial hepatectomy and cholangiojejunostomy be considered.

Since our unsuccessful experience with this procedure in infants with congenital biliary strictures,¹ the method has not been further pursued in such cases.

SUMMARY

Intrahepatic cholangiojejunostomy with partial hepatectomy was used in four adult patients in whom extensive benign biliary obstruction recurred as a result of failure of the usual methods of biliary reconstruction.

In all cases it was technically possible to perform a satisfactory cholangiojejunal anastomosis. In the selected cases in which the procedure was indi-

cated it had three advantages over the usual methods of repair (1) Less scarring and fewer adhesions were encountered in the left upper part of the abdomen than in the right (2) After exposure of the intrahepatic duct its superficial position in relation to the anterior abdominal wall facilitated the performance of an accurate anastomosis with the jejunum (3) There were not any vital structures to be avoided in the immediate operative area, such as the portal vein and the hepatic artery

One patient has been entirely well for 11½ months following operation. Two patients have been greatly improved (one for two years, the other for 13 months) but have had intermittent difficulties related to the abnormality of the biliary tract. One patient died three months after operation as a result of homologous serum hepatitis. He had made a complete recovery from the operation and was well at the time of onset of the fatal illness.

The procedure should be considered in certain cases of extensive destruction of the extrahepatic biliary system if previous reconstructive procedures have failed.

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DISCUSSION—DR. RICHARD B. CATTELL, Boston: Mr. President and Members of the Association: Dr. Walters has had a large experience in the repair of traumatic strictures of the bile ducts and as a result his report today is of particular interest to all surgeons interested in this problem. The most impressive thing has been the improvement of results in his last series of cases and particularly during the past year, for which he is to be congratulated.

There are two general operative methods that can be utilized to repair common duct strictures. The first is the anastomosis of the proximal biliary duct or ducts to some portion of the gastrointestinal tract. Dr. Walters has employed this in approximately 80 per cent of his cases and prefers an anastomosis to the duodenum. The second method of repair is the anastomosis of the proximal duct or ducts to the distal duct, thus restoring the continuity of the biliary tract with preservation of the sphincter of Oddi.

It seems to us after the experience that Dr. Lahey and I have reported on several occasions with the treatment of over 250 of these strictures that it is possible in most instances, irrespective of the amount of damage or amount of duct removed, to accomplish a duct-to-duct anastomosis. As a result of this the number of cases in recent years in which we have accomplished repair by anastomosis to the gastrointestinal tract has markedly decreased. As Dr. Lahey reported before this Association last year, there is enough of the duct within the pancreas that can be dissected up and utilized to bridge a wide defect.

Comparing our experience with that of Dr. Walters, we find that our repairs are about the reverse of his in that we do duct-to-duct anastomosis in about 80 per cent

In the smaller number of cases in which the duct is anastomosed to the gastrointestinal tract, we prefer to utilize an antecolic loop of jejunum with diversion of the tract by proximal entero-enterostomy

We are at present completing a follow-up study of our cases and find 80 per cent satisfactory results in the duct-to-duct anastomoses, whereas there has been over a 30 per cent recurrence of symptoms in patients who have had the duct anastomosed to the jejunum

It is surprising that it has taken us all so many years to appreciate the fact that reflux of contents from the gastrointestinal tract into the common duct is not responsible for recurrence of symptoms in these cases except rarely. In this, we concur with Dr Walters. If recurrent symptoms occur after an initial period of freedom of symptoms, one can be assured that there has been a recurrence of duct obstruction

In light of our experience, we would urge that a better search be made for the lower end of the common duct in the pancreas, and in spite of the fact that occasionally, even after finding such a duct, it will be impossible to utilize it, for the most part, duct-to-duct suture by this method is a feasible method of repair of these strictures

Dr Longmire's beautiful presentation of his ingenious operation of intrahepatic anastomosis of the left hepatic duct to the jejunum is of considerable interest. In view of the massive adhesions he found in the right upper quadrant in his cases, he chose this method rather than to attempt to find duct remnants. It seems to me that there are two possibilities of relief of symptoms in his cases. The first implies that there is a stump of common hepatic duct left which permits the right hepatic duct to drain through the short segment of common hepatic duct and drain back through the left duct which has been anastomosed. If this is true, there is probably enough common hepatic duct to accomplish some anastomosis directly. The second possibility is that only the left lobe of the liver is being drained. I should like to call attention to an experience we have had in six patients in whom only one hepatic duct was anastomosed when the other duct could not be found within the hilum of the liver

Surprisingly enough, with one lobe of the liver drained, two of these patients have had good results, but this has been followed by extensive atrophy and shrinkage of the opposite lobe, as we have determined on re-exploration. Based on this experience with six cases of anastomosis of one hepatic duct, I think we will need to reserve judgment on this type of operation until we have autopsy findings on these cases to show that we are actually draining both ducts by the operation which Dr Longmire proposes

DR THOMAS H. LANMAN, Boston. We at the Children's Hospital agree with Dr Walters' theory about retrograde cholangitis. In our cases of congenital anomalies of the bile ducts in which we have been able to anastomose either the hepatic or the common duct to the duodenum, we do not find that retrograde cholangitis is a problem

In our series, some cases of which have been followed for 18 to 20 years, if there is an adequate stoma, these patients do not exhibit evidence of a retrograde infection. In doing an anastomosis in these small patients it is likely that the stoma is relatively much larger than in an older patient and, of course, there is no sphincter of Oddi. We, therefore, feel that an obstructive element is the cause of retrograde cholangitis, and not a large stoma

DR WARREN COLE, Chicago. It is rather apparent from the discussion of these two papers that we must be familiar with several different types of operations when we deal with a stricture of the common duct

I think Dr Longmire's procedure is one which will definitely be of value in many cases. I have used it, but only in one patient in whom I could not find a duct at the hilum except at a distance of almost two inches within the liver. We cut across the left lobe

of the liver and encountered a fairly large duct which was anastomosed to a loop of jejunum

I agree with Dr Walters that cholangitis is in general an expression of obstruction. However, we have had two patients in whom we think we have proved that reflux did cause the cholangitis. Early in our work we anastomosed a loop of jejunum to the hilar duct in five patients, four of whom had poor results with persistence of chills and fever. I reoperated two of them within a few weeks but found the stoma between the duct and jejunum entirely patent. Since x-ray examination with barium revealed regurgitation, I decided to interrupt the ascending loop going to the hilus of the liver. The chills and fever stopped and both patients promptly got well. They had immediate relief from their chills and fever, merely by prevention of the regurgitation. We are definitely of the opinion that reflux was the cause of the cholangitis particularly since we did nothing to the stoma.

I want to call attention to a remark Dr Cattell just made on the ability to find perhaps only one duct at the hilus. We have had an experience like that in one patient, unfortunately, we found only the left hepatic duct. After looking futilely for the right duct, I anastomosed the jejunum to the left hepatic duct. Strange to say, this patient made a very satisfactory recovery and has had no symptoms whatsoever, except that she has retained a mild jaundice but with no chills and fever. I don't know what is going to happen, but she has progressed satisfactorily for two years. Dr Cattell remarked about atrophy of the other lobe of the liver, when its duct remains completely obstructed for a prolonged time. I don't know when this would take place, but already in our patient the left lobe has enlarged and the right has receded in size.

DR FRANK H. LAHEY, Boston. Dr Cattell has said practically everything we would like to say regarding our experiences with bile duct strictures, but I would like to add one or two things from the relatively large experience we have had with this very difficult problem that may be helpful to anyone who has to operate upon patients with such strictures.

I think none of us is going to fail some time or other to have to deal with these problems, and anything that anyone can add that will be helpful, just as Dr Longmire has helped in the development of his ingenious procedure, is going to be worth while.

These bile duct strictures are difficult problems. The search for the injured ducts in the scar tissue of many of these patients who have been operated upon so many times is, to say the least, a trying and a very serious problem. I would like to add just a few things out of these experiences which may be helpful to anyone operating upon patients with such strictures or duct defects.

I do not know of anything more worrisome in these cases than to open the portal vein, but having done it at least six times, I would like to give anyone comfort by saying that the pressure in the portal vein is low, and that with good exposure the portal vein can be controlled by quite rough suture. I do not think that it is something which you would want to practice every time you repair a bile duct stricture, but it is comforting, particularly at the height of the difficulty, to know that largely it is controllable.

Another thing that has arisen in my experience and in Dr Cattell's and Dr Marshall's is that we have hesitated to reoperate immediately upon these patients when they have been sent to us within a short time after the injury has taken place because of the fear of soiling and because of the bleeding and the oozing, but that is in some cases a more desirable time to operate on them than later. If you operate upon these patients soon after they have had their ducts injured, you will often have the best chance of finding cut ducts easily. The reason is that there is not then the firm scar and fixation which will be found later, the ducts are still flexible, and while the oozing and soiling make the operation anything but beautiful, they are not harmful and apparently do not interfere with the end result.

I must also reiterate that we have had to learn the very hard way to find these cut ducts in very dense scar tissue and adhesions, and I am delighted that Dr Walters has said that he is now able to find them. It means you must turn the duodenum over. You must go through all the troublesome oozing that comes from the little vessels along the edge of the mobilized duodenum. You must split the head of the pancreas. This cut pancreas bleeds distressingly, and you think it will never stop, but it always does with pressure and ligature, and with patience you can find the lower end of the duct and can, in most cases, so mobilize it that the severed ends can be approximated.

One other thing I would like to bring to your attention is the fact that in almost all cases you can fulgurate out the common hepatic or right and left hepatic ducts from within the surface of the liver. Dr Cattell has just successfully anastomosed the cut ducts in one of these patients who had had eight previous operations. I have just sent one patient home with a successful anastomosis who had seven previous attempts at repair. With patience and exposure, you can find most of these ducts and anastomose the ends.

We believe these anastomoses, particularly of the hepatic and common ducts, should be supported by a dowel in the form of a T tube for at least a year or 14 months. It is very undesirable to put the T tube through the line of anastomosis, but if you can put it below or above and have a limb of the tube go through the anastomosed area, which can and sometimes does stricture, you then keep this area open for at least a year, and I think you then have a much better chance of permanent patency of the anastomosis.

DR WALTMAN WALTERS, Rochester, Minn. I want to congratulate Dr Longmire on his excellent contribution to the surgery of stricture of the extrahepatic bile ducts.

I thought you might be interested in a cholangiogram (Fig 1) which confirms what Dr Longmire said regarding the communication between the right and left intrahepatic biliary tree. The patient whose cholangiogram is shown in Fig 1 was a woman on whom I operated twice for stricture of the common duct and was unable to find any extrahepatic duct. I inserted a rubber catheter of small size through the parenchyma on the superior surface of the left lobe of the liver into a dilated hepatic duct. The intrahepatic communication of the biliary ducts is evident in the cholangiogram and it is evident that if the left hepatic duct were anastomosed to the jejunum as Dr Longmire has shown, drainage of bile from both lobes could be obtained.

I am of the opinion that permanent results of duct-to-duct anastomosis are not going to be as good as those following anastomosis of the duct to intestine because of the danger of contracture on anastomosis of the ends of the ducts. Results were excellent in 82 per cent of my first series of cases in which the duct was anastomosed to the duodenum, in contrast to 55 per cent in which the ends of the duct were joined (Slide).

In the second series results were practically identical, they were excellent in 50 per cent of the cases in which duct-to-duct anastomosis was employed and in the other 50 per cent of these cases symptoms recurred. The percentage of excellent results was as high in cases in which choledochoduodenostomy was employed in my second series as in the first series. The similarity of these percentages in both series is significant, I believe.

Physiologically it would seem better to anastomose the duct to the duct in order to preserve the mechanism of action of the sphincter of Oddi than to anastomose the duct to the duodenum. I believe, however, that contracture is going to follow this circular type of anastomosis in more cases than we would suspect. A nonabsorbable foreign-body splint cannot be used within the common bile duct without its having to be removed later. Bile will accumulate in the interior and around any splint in the duct, whether it is a vitallium tube, a polythene tube or a rubber tube. Furthermore it will

not pass through the sphincter of Oddi unless sufficient length of tube extends beyond the sphincter so that it will be pulled out by peristalsis

In 1923 Dr McArthur of Chicago suggested the use of a rubber ureteral catheter to serve as a temporary splint for the common duct. It extends through the sphincter of Oddi, but is maintained in position with a silk suture passed through it and brought to the exterior of the body where it is anchored to a button. I have used this method in innumerable cases in which I have employed duct-to-duct anastomoses. I have kept the catheter in for as long as a year, and I think it is preferable to the T tube because



FIG 1—Complete stricture of the extrahepatic bile ducts. Cholangiogram was taken after a catheter had been introduced through the periphery and superior surface of left lobe of liver into a dilated hepatic duct. Cholangiogram shows communication between left and right intrahepatic ducts.

when the T tube is pulled out, the opening left in the duct closes by contractive fibrosis with scarring of the duct.

I think we must concentrate now on determining whether or not duct-to-duct anastomosis, and all it entails, gives superior results, which have not been apparent in my groups of cases, to the anastomosis of the duct to the intestine, and whether the anastomosis of jejunum to the stump of the common duct either with jejunojejunostomy

or a Roux-Y jejunostomy gives results superior to the more easily performed biliary duodenal anastomosis. It has been my pleasure to present the results of such operations in my cases.

DR W P LONGMIRE, JR, Baltimore. Mr Chairman, I wish to thank the discussants and to say that we have been greatly influenced in the development of this procedure by the ideas that Dr Walters has expressed for a number of years, namely, the importance of performing a careful mucosa-to-mucosa anastomosis, and the importance of such a careful anastomosis in preventing subsequent cholangitis.

We do feel that in the left hepatectomy procedure it is possible to obtain a better exposure of the end of the duct and to perform a more accurate anastomosis than would be possible when working deep in the hilus of the liver.

We have been influenced also by the statements of Dr Cole, Dr Allen and others, in regard to anastomosing the duct to a defunctionalized portion of the intestinal tract, and that accounts for the use of the Roux jejunal segment in this procedure.

We are very heartened to hear of Dr Cattell's experience with anastomosis of the left hepatic duct at the hilus of the liver. We have previously carried out some investigations to determine the portion of the liver which is drained by both the right and the left ducts, and feel that even if the obstruction were high enough to block the communication of the two ducts, a condition which we think occurs very infrequently, there is still enough liver tissue drained by the left duct that an anastomosis of this duct with the jejunum would provide adequate biliary drainage. Such seems to have been the experience in Dr Cattell's cases. Thank you very much.

DEPERITONEALIZATION CLINICAL AND EXPERIMENTAL OBSERVATIONS*

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ONE OF THE generally accepted principles of abdominal surgery is that areas denuded of peritoneum should be reperitonealized prior to closure of the abdominal cavity after celiotomy. The reason for this is the belief that such denuded areas are very likely to become the points of adhesions for loops of bowel which shortly thereafter are more firmly attached because of fibrous tissue organization of the exudate that develops between the serosa covered bowel and parietal or other area devoid of peritoneum. Such attachments are believed to favor angulations and torsions which in turn might cause intestinal obstructions.

In radical excisions of various types of large intra-abdominal neoplasms it became necessary in many instances to remove large areas of both anterior and posterior parietal peritoneum and the conditions were such that reperitonealization of the denuded areas was not possible, so that they were left bare^{1, 2}. No instances of postoperative intestinal obstruction have so far been encountered due to adhesions alone after several months to years following these operations. When obstructions have been observed, as indeed they have, months to two or more years after operation, the cause has been invariably recurrence of neoplasm in the mesentery of the bowels or between intestinal loops. Not only have anterior and posterior parietal areas been left denuded, but in over 45 instances of complete excision of pelvic viscera the entire true pelvis was stripped of its peritoneal covering, the small bowels permitted to descend into the pelvis and come into contact with the musculo-fascial and osseous surfaces of the pelvic parietes, and there have been no instances of postoperative obstruction due to adhesions.

Furthermore in over 20 additional instances where the bladder and internal female genitalia were removed with conservation of the rectal colon, but no reperitonealization carried out, there have been no intestinal obstructions. In over a hundred radical panhysterectomies with pelvic lymph node dissections and no reperitonealization of the lateral pelvic areas and areas previously occupied by the uterus and broad ligaments, there have been no instances of postoperative intestinal obstructions due to adhesions.

Failure of reperitonealization was at first not intentional, but resulted from the fact that there was not sufficient peritoneum remaining because of the wide

* Read before the American Surgical Association, St. Louis, Mo., April 21, 1949

resection necessary to excise the several types of neoplasm. It must be admitted that some misgivings prevailed at first concerning subsequent complications due to adhesions that were expected to occur. These complications did not materialize.

A series of experiments were carried out in dogs to observe what might develop in the peritoneal cavity after large areas were stripped of peritoneum or where the abdominal wound was closed without approximation of peritoneum.

EXPERIMENTAL

Dogs of both sexes and of varied breeds were employed. Operations were carried out under the usual aseptic precautions with nembutal anesthesia.

Dog 16

May 24, 1948 Segments of peritoneum on anterior abdominal wall were resected (also omentectomy and splenectomy), 14 by 4½ cm, on each side of mid-line. Fig. 1A

July 7, 1948 Celiotomy, no adhesions, denuded areas were smooth and glistening. Another area of anterior parietal peritoneum, 4 by 3 cm, was resected.

July 13, 1948 Exploratory celiotomy, no adhesions.

Sept. 24, 1948 The dog was killed. There were no adhesions to the denuded areas, the latter appeared smooth and glistening as if reperitonealized. Fig. 1B

Dog 17

May 28, 1948 A segment of the anterior parietal peritoneum was removed, 14 by 12 cm.

July 9, 1948 Celiotomy. There were a moderate number of fibrous adhesions between bowel and denuded area. There was lysis of adhesions.

Aug. 18, 1948 Celiotomy. A segment of anterior parietal peritoneum about one silk suture was removed. Several loops of small bowel were attached to the upper third of the denuded area, the remaining portion of the latter was smooth and glistening.

Sept. 17, 1948 The animal was killed. The area site of resected stitch smooth and glistening. There were many adhesions between the loops of small bowel and anterior abdominal wall.

Dog 18

May 28, 1948 A segment of peritoneum 15 by 14 cm was excised from anterior abdominal wall. The animal was killed 41 days later. There were no adhesions. The denuded surface was again smooth and glistening, and had the gross appearance of being covered with peritoneum.

Dog 20

June 15, 1948 A segment of peritoneum 14 by 14 cm was excised from the anterior abdominal wall.

July 23, 1948 Celiotomy was again performed. One loop of bowel 2 by 4 cm was fixed to the anterior abdominal wall. The remaining portion of denuded area was smooth and glistening. Adhesion was broken.

Aug. 20, 1948 Celiotomy. The denuded area was now smooth and glistening.

Aug. 28, 1948 Died (eventration). The denuded area was smooth and glistening.

Dog 22

June 23, 1948 A segment of anterior parietal peritoneum 14 by 14 cm was excised.

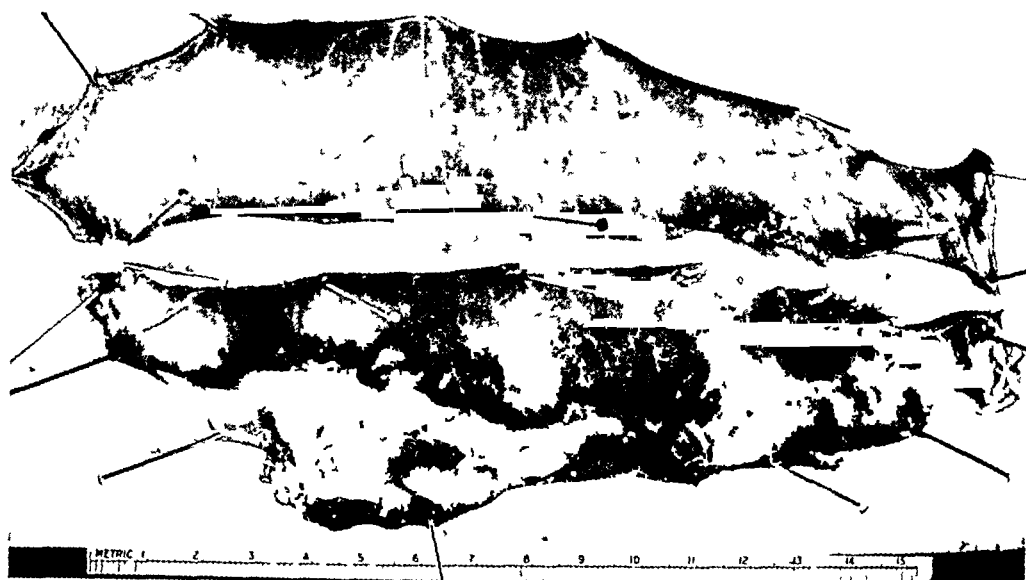
Aug. 23, 1948 Celiotomy. Adhesions between bowels and denuded area were present, but most of the latter seemed to have become reperitonealized.

Dog 021

Nov 23, 1948 A segment of peritoneum 12 by 15 cm was excised from the right anterior parietal region

Jan 1, 1949 Celiotomy No adhesions, denuded area was smooth and glistening, appeared to have become reperitonealized

A



B

FIG 1—Dog 16 (A) Photograph of two large segments of anterior parietal peritoneum each 14 by 4 to 5 cm stripped from either side of midline celiotomy wound (B) Photograph of excised segment of anterior abdominal wall taken at necropsy 4 months after initial deperitonealization and two and one-half months after second stripping of reformed peritoneum. Note smooth glistening surfaces to which there were no bowel adhesions. A new layer of peritoneum had reformed in this area

Dog 02B3

Nov 26, 1948 A segment of peritoneum 7 by 10 cm was excised from the left anterior parietal region

Jan 12, 1949 Celiotomy An area 2 by 1 cm of inferior pole of spleen was adherent to the denuded area, the remainder of the denuded area was smooth and glistening. The

DEPERITONEALIZATION

area was denuded November 26, 1948, and was again denuded of smooth glistening "peritoneum"

Feb 25, 1949 Celiotomy A small area of omentum (1 by 1 cm) was slightly adherent to the previously denuded area Bowels were not adherent The denuded areas were smooth and glistening

Dog 02B2

Nov 26, 1948 A segment of peritoneum 7 by 12 cm was excised from the mid-anterior abdominal wall

Jan 1, 1949 Celiotomy Seropurulent fluid was found in the abdomen Three loops of small bowel were lightly adherent to the denuded area and were readily freed Areas of bowel adhesions measured approximately 4 by 2, 1 by 1½, and 2 by 1 cm

March 4, 1949 Celiotomy No adhesions were noted The denuded areas were smooth and glistening

Dog 02B4

Nov 26, 1948 A segment of peritoneum 12 by 10 cm was excised from the left anterior abdominal wall

Jan 19, 1949 Celiotomy, no adhesions The denuded area was smooth and glistening It had the appearance of being covered with peritoneum

Dog 02B13

Jan 19, 1949 A segment of peritoneum 8 by 7 cm was excised from the mid-portion of abdominal wall

Feb 2, 1949 The dog was killed by another dog There were no adhesions of bowel to the denuded area, there was one thin adhesion of omentum to the denuded area Fig 2

Dog 02D7

Dec 3, 1948 The omentum, spleen and tail of the pancreas were resected The wound closed without approximation of the peritoneum

Jan 26, 1949 Celiotomy, no adhesions were present to the under surface of laparotomy wound

Dog 02D10

Dec 13, 1948 Spleen, omentum, right kidney and adrenal were resected The wound closed without approximation of peritoneum

Feb 2, 1949 Celiotomy, no adhesions were found beneath the previous wound

Dog 02D13

Jan 28, 1949 Cholecystectomy The wound closed without approximation of peritoneum

Feb 11, 1949 Celiotomy There were no adhesions to the previous wound, the underlying loops of bowel were free

DISCUSSION OF EXPERIMENTAL RESULTS

The least radical disruptions of the peritoneal surfaces are represented by Dogs 02D7, 02D10, and 02D13, in which the celiotomy wounds were closed without closure of the peritoneum at all, as a separate layer While the series is small, re-examination revealed, 54 days, 51 days and 14 days after the initial operation, no evidence of fibrous or fibrinous adhesions of bowels to the region of the operative wound, where peritoneum had not been approximated

In ten instances large segments of peritoneum were excised and subsequent reoperation in several weeks revealed no adhesions between bowels and denuded areas in six of the animals In four instances there were adhesions

In Dog 17, there were moderate fibrous adhesions between bowels and deperitonealized area 42 days after the denudation. These were severed, and at a third celiotomy, 40 days after the second, the adhesions had not recurred except for one at the site of a silk suture in the abdominal wall. At necropsy, 30 days after the third operation, many fibrous adhesions had again formed between bowels and anterior abdominal wall. In Dog 20 a large area (14 by 14 cm) had been deperitonealized, and 38 days later only one loop of bowel over an area 4 by 2 cm was adherent to the denuded area. Twenty-eight days after

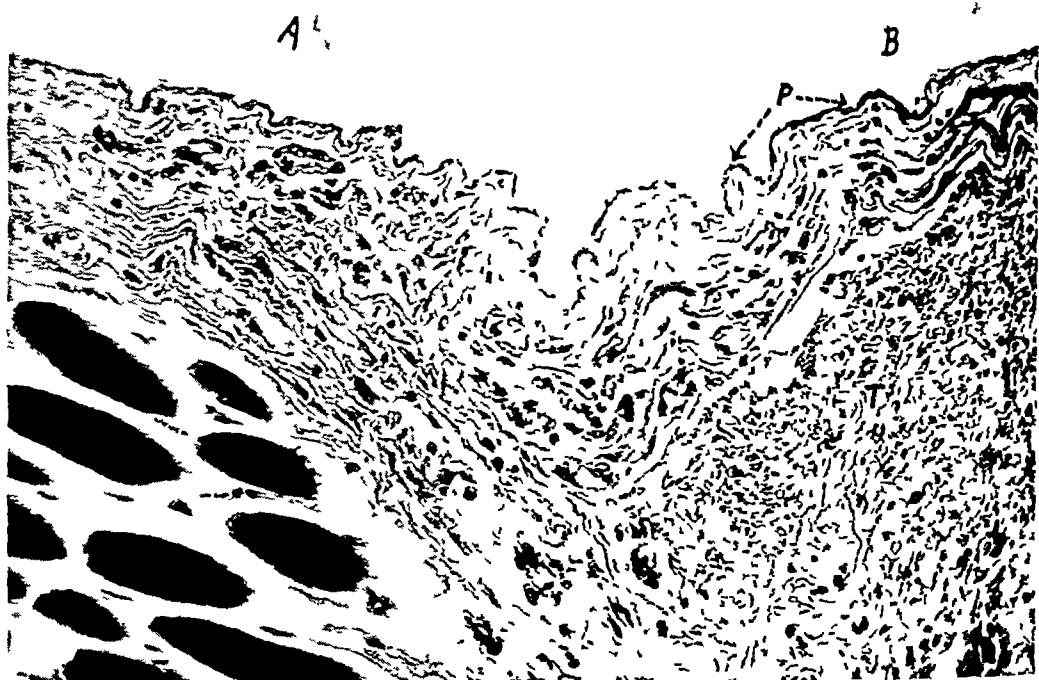


FIG 2—Dog 02B13 Photomicrograph of junctional zone between A, undisturbed peritoneum and, B, area (8 x 7 cm) deperitonealized two weeks previously. The dog had been killed accidentally by another animal and the deperitonealized area was smooth, glistening and presented no adhesions. Note P, distinct layer of peritoneum in previously deperitonealized area. T, newly found fibrous tissue in area previously stripped of peritoneum.

this had been liberated no adhesions were found, and the whole of the originally denuded area had become smooth and glistening. In Dog 22, there were fibrous adhesions between bowel and denuded area 61 days after the deperitonealization. The adhesions found in Dog 02B2 probably were stimulated, in part at least, by the chronic peritonitis present. The marked healing tendency of the peritoneum is well illustrated by Dog 02B3, where one denuded area 10 by 7 cm was created and found smooth and glistening 47 days later, at which time the same area was again denuded of reformed peritoneum and, at the third operation 44 days later, the area again found to be smooth and glistening without adhesions to underlying loops of bowel.

Microscopic examinations were made of sections taken through the areas denuded of peritoneum and which, weeks later, exhibited smooth glistening surfaces with what seemed to be reformation of a new peritoneum (Fig 2) There was loose vascularized connective tissue in these areas over which a membrane had reformed, one cell in thickness The latter cells were flattened and appeared identical with the peritoneum in the intact adjacent areas where denudation had not been carried out The mode of formation of the new peritoneum was not investigated in detail, and undoubtedly was derived from one of two sources or from both, viz, (1) proliferation of peritoneal cells from adjacent undeperitonealized areas to cover the defects, and (2) condensation of fibroblasts from the subperitoneal tissue to form new peritoneal cells in response to a functional demand

•• One feature would appear to be of special interest, and that is the situation in human patients where all of the musculo-fascial components of the abdominal wall are excised, leaving skin and subcutaneous fat only to constitute the abdominal wall During the months following such procedures the abdominal wall appears to have become thickened, denser and less elastic, indicating that the fibrous tissue elements of the abdominal wall in these areas have proliferated to add strength to the abdominal wall No hernial sacs develop, due undoubtedly to the lack of a narrow defect in an otherwise more rigid wall, the latter conditions obtaining when there is a limited separation of the deeper layers in an abdominal wound that was closed in the conventional manner, as occurs in the usual development of a postoperative incisional hernia

Two specific examples may be cited

Case 1—M D, age 53 years, admitted to Memorial Hospital in January, 1948, complaining of pain in the right abdomen, where there was also a palpable mass, obviously recurrent neoplasm invading the right abdominal wall He had previously received an excision of the cecum for carcinoma with ileo-transverse colostomy, in another institution

On March 16, 1948, celiotomy was performed and the recurrent carcinoma excised, together with the musculo-fascial and peritoneal components of the right lower portion of the abdominal wall, 70 cm of ileum that was adherent about the recurrence, the lower third of the right lobe of the liver, the upper ascending and right third of the transverse colon, and an elliptical portion of the wall of the second (descending) portion of the duodenum together with the mesenteries corresponding to the excised portions of bowel and the right kidney and ureter and retroperitoneal tissues An ileo-transverse colostomy was done The abdominal wound was closed and over most of the right abdomen the parietes consisted of only skin and subcutaneous fat

Convalescence was complicated by (a) infection of the upper portion of the wound (but no dehiscence), (b) thrombophlebitis right calf and small pulmonary infarct He was discharged on the 42nd day In a few weeks he returned to work and subsequently gained 35 pounds in weight

He was readmitted July 21, 1948, for drainage of an abscess in the right abdominal wall

By the end of a year the abdominal wall in the region where it was constituted by only skin and subcutaneous fat was, of course, more flaccid than the opposite side and yet served very well as a parietes Except for some bulging there was no frank herniation, Fig 3

On March 3, 1949, he was readmitted with clinical signs and symptoms of small bowel obstruction. Celiotomy was again performed through a right paramedian incision, and this incision was almost entirely in the area in which the abdominal wall was constituted by skin and subcutaneous fat. When the peritoneal cavity was entered there were no adhesions between the anterior parietes and the underlying loops of small bowel. The area on the right side from which all peritoneum had been stripped a little over a year previously was now observed to be covered by a smooth glistening surface which appeared

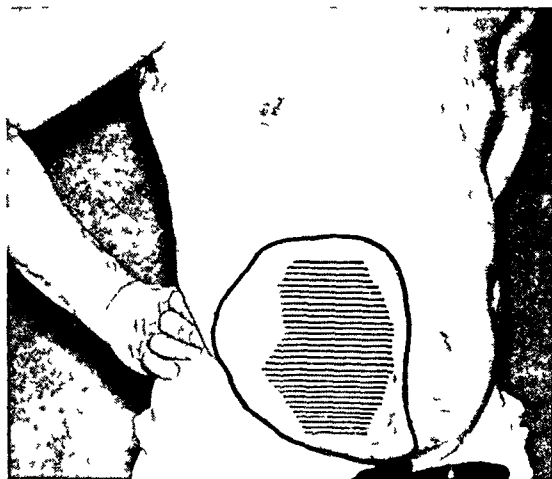


FIG 3



FIG 4

FIG 3—Case 1 M D Photograph of anterior abdominal wall approximately one year after excision of recurrent carcinoma of ascending colon that had invaded the anterior abdominal wall. Large circular marking on skin indicates the approximate extent of resection of the musculo-fascial components of the abdominal wall, and in this area the parietes were composed of skin and subcutaneous fat only. There was moderate bulging but this in no way interfered with patient's general condition, and he returned to work full time and gained 35 pounds in weight. Shaded area indicates approximate region denuded of peritoneum. A year later the patient was again operated upon for intestinal obstruction, which was found to be due to small recurrence constricting loop of ileum. No adhesions were observed between bowels and previously deperitonealized area (See Figs 4 & 5).

FIG 4—Case 1 M D Photograph was taken at celiotomy performed one year after previous excision of recurrent carcinoma of ascending colon invading right abdominal wall. At the previous operation musculature, fascia, and anterior parietal peritoneum over a large area of the abdominal wall had been excised, and the abdominal parietes in the region consisted only of skin and subcutaneous fatty tissue (See Fig 3). The above photograph was taken after a right paramedian incision. The lateral edge of the wound is readily elevated, revealing no adhesions to underlying bowel, and there has been a reformation of smooth glistening transparent surfaces identical in appearance to peritoneum.

to resemble peritoneum and, to all intents and purposes, appeared to be a new peritoneal layer that had become reconstituted in situ or by growth from adjacent peritoneal zones (Fig 4). Strips of this reperitonealized tissue were excised for fixation in formalin, and sections cut for study. Fig 5, a photograph of one of the sections, shows the presence of a veritable peritoneum.

The obstruction was found in the small bowel near the ileo-colostomy, and was due not to adhesions but to a disc-shaped mass of recurrent neoplasm that had "glued" two loops of the small bowel together with marked constriction of the lumen of one of the

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loops Resection of the involved loops, together with more mesentery and the right half of the remaining transverse colon with the old ileo-colostomy, was carried out, and a new anastomosis between lower jejunum (or upper ileum) and transverse colon just proximal to the splenic flexure was performed

Convalescence was satisfactory except for a limited wound infection

The situation in the patient described above is quite comparable to the experiments carried out in dogs, where peritoneum was excised over large areas and where, at subsequent celiotomy, no adhesions were found between underlying loops of small bowel and the denuded parietes, and where reformation of a peritoneum-like membrane occurred over the denuded area

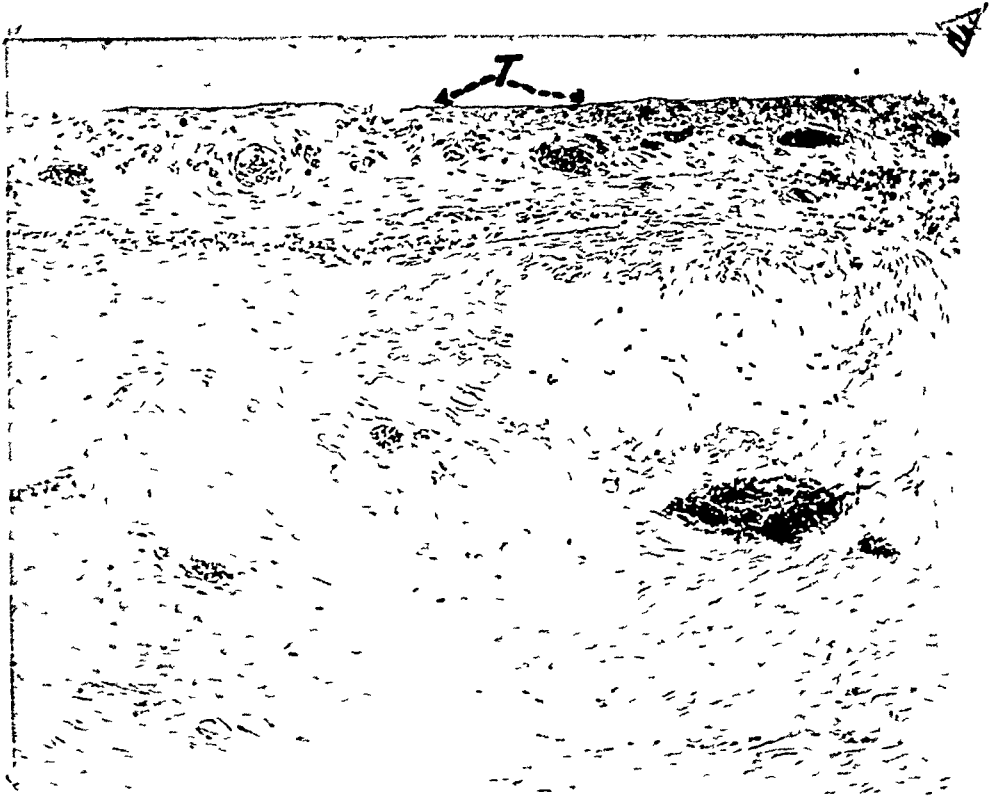


FIG 5—Case 1 Photomicrograph of peritoneal aspect abdominal wall which one year previously had been excised en masse with recurrent carcinoma of ascending colon The abdominal wall after this operation consisted of skin and subcutaneous fat only Note T, distinct layer of peritoneum that has appeared over deep surface of subcutaneous fat that was exposed to the peritoneal cavity

Another instance of good functional abdominal parietes following extensive resection of musculo-fascial and peritoneal components is afforded by the following patient

Case 2—M Y, female, age 23 years She previously had several successive resections of a neoplasm in the right lower quadrant of the abdominal wall that recurred repeatedly Histologic diagnosis Sarcoma, pleomorphic Roentgenray therapy had also been given

On June 27, 1947, a wide resection of the musculature and fascia of the right lower abdominal wall was carried out, the incisions encompassing widely the gross limits of the tumor When the peritoneal cavity was entered it was observed that the cecum and ascending colon were adherent to the deeper surfaces of the tumor Accordingly a right hemi-colectomy was performed en masse with the segment of right abdominal wall Closure of the wound was carried out in such a manner that only skin and subcutaneous fat formed the abdominal wall over a large area of the right lower parietes The general

condition was very satisfactory after operation, and during the ensuing months the portion of abdominal wall mentioned above became somewhat rigid and did not bulge unduly when the patient coughed. She was seen again a year and a half after the initial operation, she was six months pregnant and roentgenograms of the chest revealed diffuse metastases in both lungs. General deterioration had not yet begun to manifest itself. The right lower portion of the abdomen continued to appear firm and there was no excess bulging (Fig 6)



FIG 6—Case 2 M Y Photograph of abdominal wall a year and a half after extensive excision of musculature, fascia and neoplasm (sarcoma) of lower right quadrant, together with right colon adherent to under surface. An elliptical portion of the skin was also excised. Outline on skin indicates the approximate extent of musculo-fascial resection and in this area the abdominal parietes consisted of only skin and subcutaneous fatty tissue. Shaded area indicates approximate extent of peritoneal denudation at the time of the operation. Photograph taken at sixth month of pregnancy, and at this time there were bilateral pulmonary metastases, but the patient's general condition remained satisfactory.

COMMENT

That adhesions may occur following celiotomy, and that these may subsequently give rise to intestinal occlusion or be the cause of volvulus, needs no comment or elaboration. This is a long recognized fact. The cause of such adhesions, however, is probably not as readily explained as might be generally supposed, *i e.*, on the basis of trauma to peritoneum, or defects in peritoneal surfaces, the healing of which leads to adhesive bands to underlying loops of bowel.

It would appear that denuded parietal surfaces in the peritoneal cavity readily heal by proliferation of peritoneum at the margins of the area and/or by condensation of connective tissue in the denuded area to form a new smooth glistening surface membrane (peritoneum). It would appear that such reconstitution of peritoneal surfaces is the normal sequence and that this readily occurs unless other factors supervene. Among the latter may be mentioned infection, which stimulates fibrous tissue reaction and possibly interferes with the reappearance of the condensed superficial layer of tissue (peritoneum). Furthermore, there is the as yet undefinable tendency in some individuals to react to trauma by overproduction of fibrous tissue with dense collogenic interstitial substance.

The studies cited in the above report are not interpreted to indicate that complete disregard for reperitonealization is advocated. They are interpreted as suggesting that reperitonealization is not of sufficient importance to weigh heavily in determining the mode of procedure for radical extirpation of abdominal malignant neoplasms and that when reperitonealization of certain areas is not possible and is not carried out, this factor alone should be of no great concern in regard to possible subsequent development of adhesions which in turn may lead to angulation of bowel with occlusion or to volvulus of one type or another. Furthermore it may be inferred that after a complex and lengthy procedure, prolongation of the operation for meticulous approximation of the peritoneal layer in wound closure is not important enough to appreciably delay termination of the procedure and return of the patient to bed.

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DISCUSSION—DR HARVEY B. STONE, Baltimore. Mr. President and Members, I agree with the comments and the very interesting reports of Dr. Robbins and Dr. Brunschwig concerning excisions and removal of the parietal peritoneum. It has been my experience in excisions of the right side of the colon and of the left side of the colon that I was unable to do what I was directed to do by many authorities on this subject, namely, cover this defect by transplantation of peritoneum, because the defect extended often from the diaphragm to the brim of the pelvis and from the midflank line to the lateral margin of the vertebra, and in my hands, at least, there wasn't a possibility of covering the defect.

With considerable trepidation I permitted this raw space to remain for lack of anything to do about it, and discovered in a number of subsequent explorations of such abdomens that there was not, as the essayist has described, any extensive development of adhesions between the movable viscera and this denuded area, and that it had covered with a glistening surface which was to the naked eye undifferentiated from the rest of the peritoneum.

However I think we must be careful in drawing inferences too broadly from what has been said. I would like to have in the published paper a little clearer distinction made between raw surfaces of a parietal nature and those of visceral nature.

Nothing in my experience—and, I must add, nothing in the experience as presented by the essayist—controverts the established principle that raw surfaces of gut and omentum are prone to develop dangerous adhesions with consequent obstructive conditions resulting, and that one must sharply distinguish between the importance of raw surfaces of parietal nature and of visceral nature, and that it is still imperative in good surgery to do what may be done to protect these raw surfaces of a visceral nature

I should like to call attention to a recent article by Dr Jere Lord and his associates in which he called attention to the Noble maneuver for plicating raw surfaces of peritoneum so as to self-cover the denuded surfaces I believe that is a method which deserves much wider recognition than has been accorded it

Mr President, I am about to do something which I realize has no justification I want to say that while I agree with what has been said about the significance and importance of raw surfaces of parietal peritoneum as related to these extensive operations, I would not like to be understood as agreeing that these operations in themselves are always desirable or defensible

If I may extend the field of discussion a bit, I should like to call your attention to the fact that there is now a widespread tendency to extend tremendously the anatomical scope of attacks on cancer There are certain things that I think we need to sharpen our thinking about in this regard

In the first place, these procedures are not new methods of treating cancer, they are simply extensions of the accepted method, which consists of ablation of structures which are involved or may be involved in cancer It is the best way we have at present for treating cancer, and our best is a very poor best We must admit that This new extension of the accepted principle of destruction is in no sense a new attack on the cure of cancer

We are asked to extend these procedures to a degree which approaches what the economist speaks of as the point of diminishing returns, even though it be accepted that there is a salvage, a small percentage salvage, among the victims, shall I say, of these extensive operations One has to weigh against that salvage the loss of function, the mutilation and the deterioration of health which often results It is a question of balancing the possible advantages of salvages of these procedures against the increased mortality and increased morbidity and increased mutilation

An analogy was made yesterday in one of the talks between the search for the last residual node and the attempt of a bird dog to go through a barbed wire fence to get a bird I would like to suggest that the occasional bird which is recovered perhaps would not compensate the farmer for the destruction of the fence

I think it might be well for us to balance these things carefully, and, shall I say, conservatively (that is a terrible word to use) before we commit ourselves too generally to this type of surgery

DR OWEN H WANGENSTEEN, Minneapolis, Minn Mr Chairman and Gentlemen, we have all listened with much interest to the presentation by Drs Brunschwig and Robbins They put the larger emphasis on the question of intestinal obstruction That obviously is a matter of some importance—but I would think the larger question of importance would be how the absence of wide areas of peritoneum influences the healing of intestinal anastomoses

A number of years ago, when we were toying with the elective primary intestinal resection in strangulated intussusceptions, Dr W P Ritchie and I extraperitonealized an anastomosis which we had made in an infant, not being certain that it would be a good thing to leave it in the peritoneal cavity We had planned to drop the anastomosis back into the peritoneal cavity About the fourth day, however, Dr Ritchie discovered a leak in it Another of my associates, Dr R E Burge, then in the Experimental Surgical Laboratory, made a number of extraperitoneal as well as extracutaneous

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anastomoses, leaving the blood supply intact. These anastomoses all leaked. I believe the peritoneum affords an anastomosis some protection against leakage. I am not talking about the loss of peritoneum after hemicolectomy. My reference is to instances in which peritoneum is excised over large areas—operations in which the greater portion of the posterior parietal peritoneum to the lower abdomen and pelvis is sacrificed in the excision of large adherent cancers in the lower abdomen, and cases in which intestinal anastomoses are made in that area.

I have the feeling that one may leave such an operation with a greater sense of security with reference to the healing of single or multiple intestinal anastomoses if there is peritoneum there. I would like to ask Drs. Brunschwig and Robbins if they have had occasion to feel that extensive deperitonealization vitiated the healing of intestinal anastomoses made in the immediate vicinity of the deperitonealized areas.

For a number of years in patients upon whom I have found it necessary to excise large areas of peritoneum in the pelvis in the presence of concomitant intestinal anastomoses, I have employed a loop of the terminal ileum and its mesentery to reperitonealize the pelvis and to construct a new pelvic peritoneal floor. In concomitant excision of the uterus and pelvic organs, when the rectum is amputated in its mid-portion, such a loop can be applied against the posterior aspect of the coloproctostomy. This maneuver applies a supporting tissue to that anastomosis, at the same time it provides a means of reperitonealizing the posterior portion of the abdominal wall after sacrifice of its peritoneum. One can take this loop, suture it here and there, fan the mesentery out, and make an entero-anastomosis proximal to the cecum. This loop empties itself and covers the whole denuded area very nicely, moreover, it affords protection against leaks to any juxtapositional intestinal anastomoses.

All of us know that a dry wound is essential to healing, whether it be in a tooth socket, the pleura, the abdominal wall, or in the peritoneal cavity. If an anastomosis hangs suspended in a free space, unsupported by pliable tissues, it is not going to heal very well. I do not believe we should discount protection to intestinal anastomoses of adjacent peritoneum.

There are three operations which many of us do frequently, in which we do not rely too much upon available serous surfaces. One is a thoracic esophageal anastomosis. However, if we can mobilize pleura or the pulmonary ligament to cover the anastomosis, we feel better about it. The second is the Finsterer antral exclusion operation. The third is an extra or subperitoneal anastomosis of the rectum. Yet, in all these procedures, if we can cover or support the anastomosis with an available serous surface, I believe all of us feel that there is less risk of a leak in the anastomosis.

Now, I would like to speak briefly about this matter of a more radical operation. It is true, as Dr. Stone stated, that the salvage in late cancer is small. You will remember the Biblical admonition concerning the interest of the shepherd in the one sheep that had gone astray. Banks offer us one per cent on our money. Our discussion concerns the most valuable thing that people have—their lives. Until we are able to diagnose cancer early, we shall have to continue to manifest an aggressive surgical attitude toward cancer. There is no other satisfactory treatment in the majority of instances. And the salvage, even in late cases, is far greater than the one per cent current interest rate on money.

Until we have specific organ diagnostic technics or acceptable biologic tests for cancer, surgeons must continue to stress the importance of Cancer Detection Centers in the early recognition of cancer. Cancer is frequent, it is merely a question of (1) Who will have it? (2) When? and, (3) In what organ?

I cannot agree with Dr. Stone that we should retrench rather than continue to pursue an aggressive attitude toward late cancer. To be sure, most of our efforts in late cancer are palliative. In gastric cancer in which the local lesion is excised, and in which hepatic metastases are present, the expected mean survival is 20 months in

our clinic I have asked many a man if he has considered that reprieve worth while. The answer has always been in the affirmative. In this Voyage of Life, who expects to reach the other shore? We are all condemned to death, it is only a question of how long execution of the sentence may be delayed. Since man was driven out of the Garden of Eden, no one expects to live forever. It is our responsibility to make lives longer and happier if we can. Even old people who have been operated upon for cancer, in my experience, want to keep their frail vessels in this Voyage of Life afloat just as long as the voyage and the weather are pleasant.

There is an extension of operation in abdominal cancer which my colleagues and I have begun to explore, viz. re-entry of the abdomen after a period of four to six months in Group C lesions (patients with lymph node metastases) to do a wiping out operation. As yet, our experience is not large. But why wait 15 to 20 months for the reassertion of symptoms? That is the usual length of the silent interval in cancer.

The impress of surgeons upon the cancer problem is beginning to be felt. We must not lose heart, we must go ahead. We surgeons must continue a live interest in the cancer problem until help is available to us from other sources. When surgeons have the opportunity to operate largely on Group A or Stage I cancers, the late results of cancer surgery will begin to compare favorably with the results of surgery for benign conditions.

DR JONATHAN E. RHOADS, Philadelphia. I would like to refer briefly to some experiments on the formation of adhesions which Dr. Chandy, Dr. Portnoff, Dr. Jackson and I carried out in rats. We found not only that parietal peritoneum would regenerate but also that visceral peritoneum, if removed delicately and without injury to the deeper layers, would regenerate very well also.

If a fine silk suture was placed under the peritoneum of the rat and not tied, it would usually be sealed over without the production of an adhesion. However, when fine silk sutures were placed and tied, so as to oversew superficially denuded areas on the cecum, adhesions were frequently encountered. In fact, they were more frequent than when such areas were not oversewn but allowed to heal spontaneously.

One cannot apply conclusions from animal experiments to clinical practice without substantiating experience yet, in view of Dr. Brunschwig and Dr. Robbins' observations on the parietal peritoneum of patients, the problem of managing superficial injuries to visceral peritoneum in man should at least be reinvestigated. It may be that repertonealization in patients would occur spontaneously with less adhesion formation than when sutures are used.

DR JOHN C. BURCH, Nashville. It is perhaps unfortunate that the magnitude of Dr. Brunschwig's palliative operations has drawn attention from a more fundamental aspect of his work. I refer to his attack upon cancer of the cervix. At the present time this disease is killing about 25 out of every thousand women. By his broadening of the operation it is certainly possible that curative surgery can be attempted in certain cases now considered inoperable and palliative treatment can be achieved in an even larger number. For this I think Dr. Brunschwig is to be congratulated.

DR ALEXANDER BRUNSCHWIG, New York City. I want to thank those who discussed our paper for their remarks.

The point raised, which I think was very well taken, was that we are talking about parietal peritoneum and not visceral peritoneum.

The reference to the Noble procedure is pertinent. It is an operation that should be carried out perhaps more often than it is when conditions indicate it.

As long as Dr. Stone has raised a question concerning radical resections in general, I want to make a statement or two, but I do not wish to prolong this into a

discussion that could last for perhaps an hour, and besides it is not pertinent to our paper

I think his words of warning are timely since radical excisions of advanced cancer are not to be undertaken lightly. About four years after Billroth first described gastrectomy, Welch, the late great pathologist at Hopkins, wrote a paper enumerating seven or eight reasons why gastrectomy was bound to be a futile procedure, pointing out that surgeons would never encompass gastric cancer by surgery and intimating that surgeons were indeed presumptuous in trying to do so. For almost every extension of surgery the same arguments can and have been raised.

In 1895 Nicholas Senn stated in his book on "Tumors" that he thought surgeons had gone too far in attacking cancer of the pylorus because he had operated on 16 and they had not survived, obviously due to the very poor supportive treatment available at the time.

For patients who have large cancers in the abdomen there is only one chance for prolongation of life and that is to get the tumors out. Whether one wants to take the chance, I think, is up to the individual surgeon in his attitude toward operating for cancer—some may be defeatists, others not. Some of you know that we reported 100 consecutive cases of so-called inoperable cancer, in a monograph*. I can report now the long-range results.

Thirteen of those patients, or 13 per cent, are living and well for over six years—after operation. They are not derelicts, they are not vegetables, but they have returned to useful, active lives.

Thirteen per cent is not a great salvage rate. This does not include an additional 6 per cent who survived an average of over three years and returned to normal useful lives. I should like to emphasize again that this is a series of patients that were selected for their *poor condition* rather than their favorable condition for surgical attack. If we consider *all* patients with gastric cancer that walk across the threshold of any clinic, I doubt whether we can be sure that we can salvage 13 per cent for six years, and among these would be a fair number of so-called favorable cases. In the series of 100 patients that I just alluded to, there was not a single "favorable case" and among them are included patients who had been explored elsewhere with nothing done because the situations encountered conformed to the classical criteria of inoperability.

* Radical Surgery in Advanced Abdominal Cancer. University of Chicago Press, 1947.

INTESTINAL OBSTRUCTION IN THE NEWBORN*

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IMPRESSIVE STRIDES have been recorded in intestinal surgery during the past quarter of a century, due to improved diagnostic aids, decompression of dilated intestinal loops by intubation, control of infection, more effective supportive therapy, and somewhat better operative technic. During the same interval the chance of survival of the newborn infant with intestinal obstruction has increased but not to a degree comparable with the improved prognosis of the adult.

Twenty years ago only a few cases of intestinal obstruction in the newborn due to anomalies had been successfully treated. Just ten years ago Dr Edwin M. Miller¹ reviewed the subject before the Association and reported several successful cases. In the discussion of Dr Miller's paper, Dr William E. Ladd reported 24 recoveries out of 29 cases of extrinsic obstruction and eight recoveries out of 17 cases of intrinsic obstruction from the Boston Children's Hospital. The best published figures to date are those of Ladd,² who in 1943 recorded 59 cases of extrinsic obstruction with 37 recoveries, and 87 cases of intrinsic obstruction with 23 recoveries. It would be impossible to overestimate the influence of the Boston Children's group upon the surgery of infants and children during the past three decades.

Within the past ten years a number of cases successfully operated upon have been reported by Arnheim,³ Biggs and Pontius,⁴ Bush et al,⁵ Donovan,⁶ Duncan et al,⁷ Duckett,⁸ Erb and Smith,⁹ Gomez and Lozoya,¹⁰ Judd,¹¹ Lyons and Brenazzi,¹² Martin,¹³ Medearis,¹⁴ Miller et al,¹⁵ Potts,¹⁶ Thompson,¹⁷ Wickle,¹⁸ and Wright.¹⁹

That recoveries are no longer rarities does not, however, minimize the fact that the mortality of intestinal obstruction in the newborn remains high. Since means of decreasing mortality now seem available, a critical analysis of our failures, with a view to developing a more systematic approach to the problem, particularly from the standpoint of the surgeon, would appear to be of value. The series of cases presented by the authors shows mortality figures which are far from impressive. The patients were cared for by a number of surgeons in three large general hospitals. Analysis of the cases forms the basis for the observations and recommendations of the authors.

The most pertinent causes of mortality in the infant with intestinal obstruction are the following:

1. Many of the babies with intestinal anomalies are born prematurely and are poor candidates for any sort of operative procedure. The coincidence of

* Read before the American Surgical Association, St. Louis, Mo., April 21, 1949

other anomalies in these infants is also high. As surgeons we can offer little help to improve this factor. The prevention of premature births by the obstetrician and the internist may significantly alter these figures in the future.

2 *Delayed operation*, due to inaccurate or *tardy diagnosis*. This is probably the most important preventable factor in the high mortality. Many of these delays are chargeable to the obstetrician or the pediatrician but many are due to indecision on the part of the surgeon. The improved mortality that goes with earlier recognition and earlier operation is demonstrated in the tables presented.

3 *Inadequate supportive therapy* is probably the next factor of



FIG 1—Case 6 Typical gas shadow of the dilated stomach and duodenum of complete atresia of the duodenum proximal to the ampulla of Vater



FIG 2—Case 3 Atresia of duodenum proximal to the ampulla with perforation and pneumoperitoneum. The roentgenograms show the distended stomach and duodenum as though suspended in gas within the peritoneal cavity. The collapsed small and large intestines can be seen. No contrast media necessary.

importance Shock and peritonitis have in the past, contributed heavily to the mortality

4 *Operative indecision* and unphysiologic operative measures are about as important as inadequate supportive therapy in contributing to the mortality

DIAGNOSIS

Early diagnosis merits special emphasis Vomiting in the newborn infant is too common to cause concern but when the vomitus contains bile and when the abdomen is distended on the first day of life, the diagnosis should be considered to be intestinal obstruction due to an anomaly until proved to the contrary The acceptance of this simple, didactic statement literally would save many lives Very few babies who vomit soon after birth due to functional

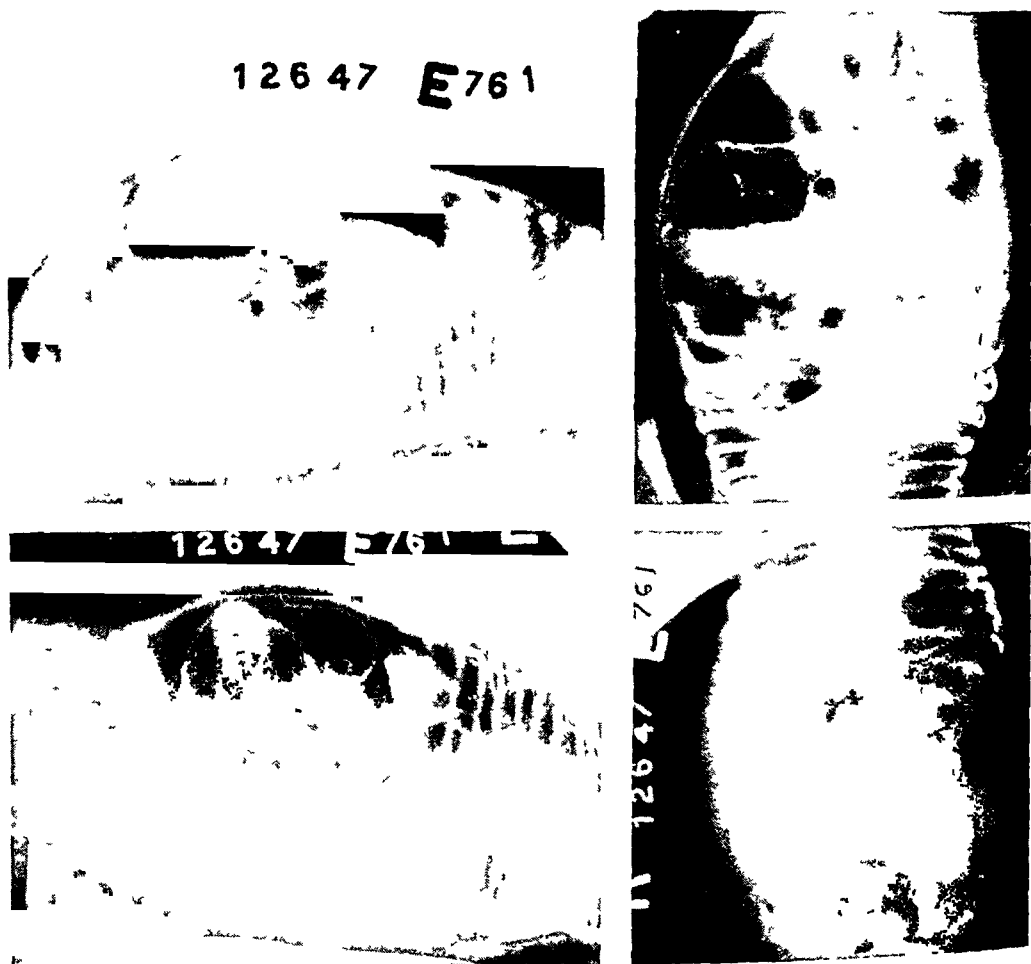


FIG. 3—Case 17 Ileal atresia with perforation Plain roentgenograms in four different positions show multiple distended and gas-filled loops of small intestine, fluid levels within the loops and also free in the peritoneal cavity, and pneumoperitoneum

causes show abdominal distention When the abdomen is tightly distended, furthermore, with tympany that obliterates liver dullness, with shiny skin and dilated superficial veins, the diagnosis of intestinal obstruction with perforation, pneumoperitoneum and peritonitis is almost certain Symmetrical distention of the abdomen, in the absence of pneumoperitoneum, usually implies

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obstruction in the jejunum or ileum. Distention of the upper abdomen alone implies duodenal obstruction. Visible peristalsis is often apparent, coursing from left to right over the upper abdomen, especially when obstruction is in the duodenum or upper jejunum. The absence of bile in the vomitus does not rule out obstruction, since the point of atresia or stenosis may be proximal to the ampulla of Vater. Visible peristalsis is likely to be present in such cases. The presence of visible peristalsis within a few days after birth almost always indicates the presence of congenital obstruction in the upper intestinal tract. Pyloric stenosis occurs so rarely at this age as to be statistically insignificant.

The vomiting of meconium-like material is usually indicative of a duodenal obstruction. In case No. 3 the vomitus and the stool appeared almost identical. In several of our cases the vomitus contained gross blood. With the obstruction in the jejunum or ileum the vomitus is more likely to be of an intestinal character. The lack of milk curds in the stool of the newborn infant is also diagnostic evidence of importance. The stool of a normal infant on breast or formula begins to show some milk curds within the first 24 hours, or at the latest, on the second day of life. The absence of such findings may be considered evidence of complete obstruction. Fairber's²⁰ test, showing the presence or absence of cornified squamous epithelial cells in the stool, may be of some help in determining the continuity of the intestinal tract, as is the absence of bile in the stool, but other criteria have seemed more certain to us.

Vomiting due to intrinsic obstruction occurs almost always during the first day of life and is continuous from that time on. If obstruction is due to extrinsic factors alone, however, vomiting may not start on the first day and it may be intermittent, and part of the feedings may be retained for days or even weeks after birth (Cases Nos. 36, 7, 42). In cases of extrinsic obstruction due to errors of rotation it is common to have the baby pass normal stools for several days, decreasing in amount as the degree of obstruction increases. If the obstruction is low in the colon, vomiting may not start for several days after birth. Except where obstruction is high in the duodenum, vomiting is not likely to be projectile.

In addition to the evidences already mentioned, the distended stomach and



FIG. 4.—Case No. 45. Three-day-old infant with stenosis of the duodeno-jejunal junction. The duodenal gas shadow fills the entire abdomen. The stomach is small in size and contains only a little barium. This is a very unusual picture.

duodenum, or loops of ileum, usually can be palpated through the thin abdominal wall unless obscured by pneumoperitoneum or diffuse peritonitis

The plain or "flat" roentgenogram of the abdomen is unquestionably the most helpful diagnostic aid in intestinal obstruction of the newborn that is available. It is usually possible to identify the gas-filled viscus and its location, with sufficient accuracy to provide approximate localization of the point of obstruction. The plain roentgenogram will almost always make the diagnosis of duodenal or intestinal atresia apparent (Figs Nos 1, 2, 3, 5). Information may be obtained from films taken in different position, and by injecting air into the stomach after evacuating the contained fluid.

When the diagnosis is quite clear from the clinical evidence and from the plain roentgenogram, the use of barium is to be avoided since its presence in the intestine may complicate the postoperative course. When the diagnosis is



FIG 5

FIG 5—Case 18 Atresia of the distal ileum. The roentgenogram shows the distended loops of small intestine and also shows the colon to be in approximately normal position but of small caliber.



FIG 6

FIG 6—Case 20. The roentgenogram shows marked distention of the entire colon due to stenosis of the sigmoid.

not complete without barium, however, its use is definitely indicated. The barium enema alone may be very helpful in identifying the approximate level of the atresia in the ileum (see Fig 5), or to demonstrate the presence of a colon on the left side of the abdomen, in cases of malrotation (Fig 7), or to distinguish between colon and distended ileum (Fig 6). The diagnosis of extrinsic obstruction due to errors of rotation may not be possible from the plain roentgenograms alone and here a small amount of barium by mouth, with or without the addition of barium by rectum, may greatly simplify the diagnosis (Figs 7, 8).

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In short, the history of vomiting bile soon after birth, together with abdominal distention and abdominal gas shadows in the plain roentgenogram, are usually sufficient to make a presumptive diagnosis of intestinal obstruction due to a congenital abnormality

SUPPORTIVE THERAPY

It is axiomatic that the small infant tolerates blood loss, shock and dehydration poorly, and these factors are all operative in the newborn with intestinal obstruction. Our ability to give adequate quantities of whole blood to the babies, before, during, and after operation, together with the ability to control postoperative infection with antibiotics, has greatly widened the limits of operability

It is to be assumed that the baby with congenital intestinal obstruction will have been maintained on parenteral fluids since birth. The newborn infant, if born at term, will tolerate two or three days of starvation and moderate dehydration, but many infants with anomalies are born prematurely and for

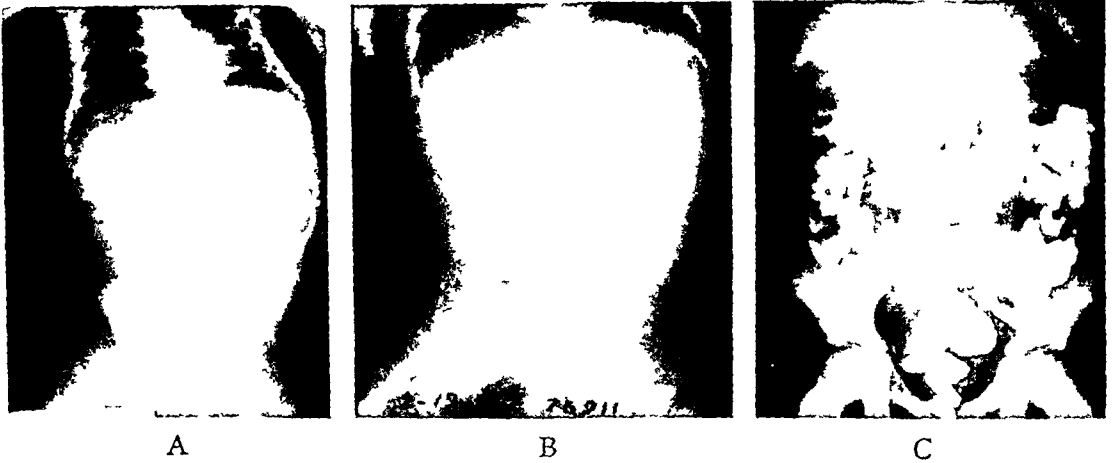


FIG 7—Case 29 Malrotation and volvulus. A shows the typical picture with barium in the dilated stomach and a gas-filled duodenum, with only a few flecks of gas below. B shows that a few flecks of barium have passed into the jejunum. Barium enema given at the same time shows a diminutive colon entirely on the left side, a fact which practically clinches the diagnosis. C shows the same child at six years of age. Barium enema shows the colon in normal position. In this case the cecum was placed upon the right side at operation.

them the period of starvation is a much more serious one. During the interval between the time a surgeon makes the diagnosis and the time of operation, as much parenteral physiologic fluid should be administered as will be absorbed. If the baby is obviously depleted, time will be well spent in giving a blood transfusion of 75 to 100 cc of whole blood slowly, following with an equal amount of electrolyte solution. The surgeon should not make the incision in the abdomen until a needle is in a vein, or in the bone marrow, and blood is running satisfactorily, no matter how good the patient's condition may seem to be. Unless this absolute rule is followed, the surgeon may find himself engrossed in untangling the anomalous situation of the intestinal tract only to discover that the baby is in severe shock and the anesthetist and

assistants are unable to get blood started. It is advisable to leave the cannula or needle in the vein or bone marrow after operation and continue either blood or electrolyte solution as indicated, at a slow rate, for some hours after operation.

While it is felt that intravenous transfusion is generally preferable, technical considerations occasionally make bone marrow transfusions the method of choice, both during the operation and subsequently. Bone marrow infusions are not without danger (see Case No. 17) but offer the advantage of being able to use the same site for repeated injections. Whether or not permanent injury can be done to the bone marrow cavity of the long bones in this manner is still open to question. When the infant's life depends upon blood transfusion in a hurry the bone marrow route offers obvious advantages.

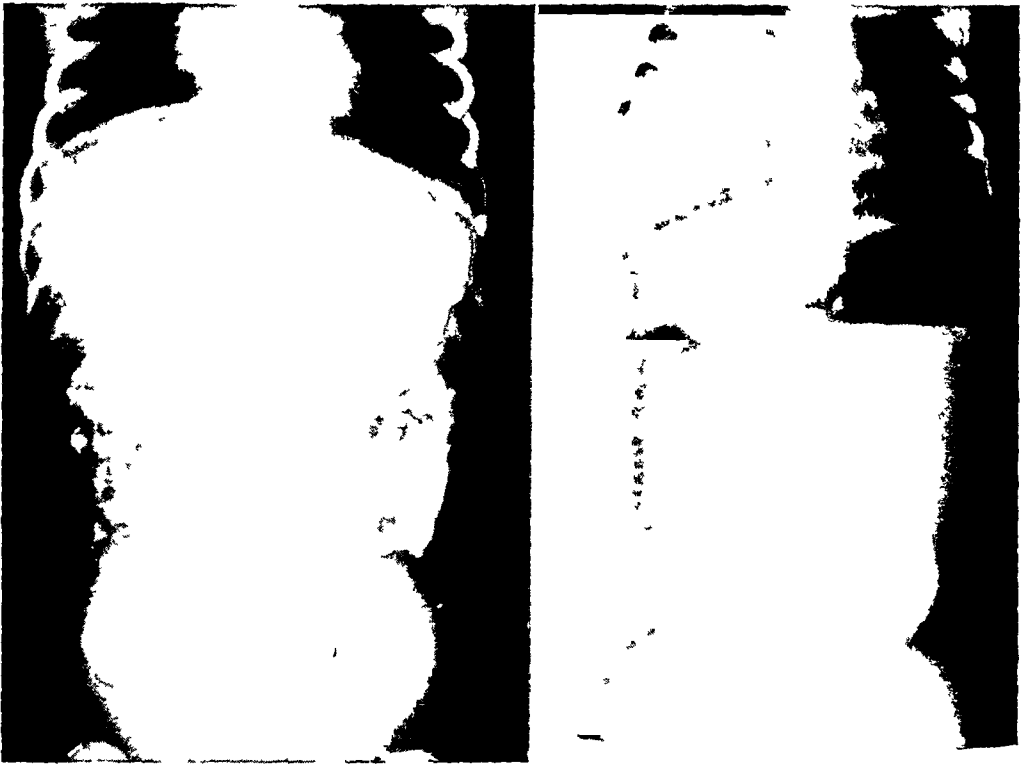


FIG. 8—Cases 37 and 38. These two roentgenograms show the extremes of findings in cases of malrotation with volvulus. Case 37 on the left, who was operated upon at six days of age, shows considerable barium in the small intestine as well as dilated stomach and duodenum. Case 38 on the right was operated upon at two days of age, and on the plain roentgenogram shows the two large gas bubbles and fluid levels characteristic of duodenal obstruction, but no gas in the intestine. Both recovered.

After operation the problem of maintaining fluid and protein balance is often difficult, especially if fluid is being lost from a temporary enterostomy or by rectum due to a short-circuiting operation. Under such circumstances the management of replacement therapy becomes an exacting problem which requires the most careful supervision of the pediatrician and surgeon. Day

to day observations on the relation of intake to output, cytological and chemical blood examinations are required if serious depletion is to be avoided. The earlier that the needs of the infant can be met through protein-containing fluid absorbed from the intestinal tract, the less the danger of serious imbalance.

Penicillin seems to be the antibiotic of choice for routine use. We prefer to have penicillin given intravenously prior to and during the operation in order to maintain a good blood level when the peritoneum is opened. In cases of resection, anastomosis or other potential source of contamination of the peritoneum, penicillin is continued for several days. If there is at any time evidence that infection is not controlled by penicillin, or that the causative organism is penicillin-resistant, other antibiotics are used. Because of its low toxicity, penicillin seems to be most desirable for routine use in newborn infants.

OPERATIVE MANAGEMENT

Anesthesia, incision and extent of exploration. The junior author prefers ether anesthesia and a right rectus incision. The senior author prefers procaine ($\frac{1}{4}$ per cent) anesthesia and a transverse incision, upper right for duodenal lesions and lower right for lesions in the ileum or colon. We both feel however that the matters of anesthesia and incision are very personal ones with the operator and, particularly when operating on babies in precarious condition, the surgeon should use the method of approach with which he feels most comfortable. The combination of anesthesia and exposure which makes it possible for the surgeon to explore the abdomen thoroughly with minimal trauma and loss of time, and to do a definitive operation accurately, is the optimum. When a surgeon who is accustomed to working under general anesthesia attempts to use local anesthesia on a difficult case, he is likely to be handicapped and the patient is likely to suffer.

In the years before adequate supportive measures were available, we often attempted to correct the cause of obstruction through a small incision without thorough exploration. We now feel that such an approach is wrong. With the available methods of preventing and combatting shock and infection there are very few infants, whose condition justifies any attempt at operation at all, who cannot tolerate thorough exploration. We feel strongly now that the abdomen should be explored thoroughly regardless of the cause of the obstruction or its apparent ease of correction. The incidence of multiple causes of obstruction is high. (Cases 15, 31, 43, 44, 45.) Incomplete exploration ranks high as one of the causes of failure in our series, as well as in other reported cases.

Assessing the probabilities. The surgeon must be aware of certain fundamental facts and probabilities before he opens the abdomen, these may be summarized in simplified form as follows:

1. The common sites of atresia or stenosis are (a) the second part of the duodenum, near the ampulla of Vater, (b) the duodenal-jejunal junction (which is also the site of obstruction due to congenital bands retroperitoneal

hernia and volvulus due to malrotation), (c) the distal ileum, (d) the distal colon and rectum

2 Ring pancreas alone may cause obstruction, but it is often accompanied by intrinsic obstruction of the duodenum (Cases 1, 7)

3 The majority of congenital obstructions of the duodenum are distal to the ampulla of Vater

4 Incomplete rotation with partial or complete volvulus usually causes obstruction at or near the duodenal-jejunal junction

5 Incomplete rotation often occurs concomitantly with atresia or stenosis of the duodenum or ileum. It is important to remember that release of the volvulus due to malrotation does not fulfill all the requirements for complete operation unless it is clearly demonstrated that no other obstruction exists by passage of a catheter or Levine tube through the duodenum into the jejunum

6 The incidence of multiple points of obstruction is sufficiently great to demand thorough exploration in every case

7 Defects in the mesentery, bands and points of irregular fusion of the peritoneal layers which are capable of causing obstruction often accompany malrotation (Cases 30, 42, 43, 44)

8 Marked dilatation of the colon occurs in the presence of atresia or stenosis of the distal colon (Case 20). This is a rare finding

TECHNICAL CONSIDERATIONS

Operation is always performed with a small Levine tube or catheter (No 8 or 10 French) in the stomach for the purpose of constant decompression. Before opening the peritoneum the surgeon has made a tentative diagnosis on the basis of the criteria previously mentioned, and the incision is planned accordingly. Upon opening the peritoneum, one or more of the following alternative findings will immediately present

1 The presence of free gas and fluid in the peritoneum necessitates an immediate search for the point of perforation in order to avert further peritoneal contamination. The most likely point of perforation is the ileum and the next most frequent is the second part of the duodenum. If the small intestine is dilated it should be delivered immediately to control the point of perforation. If the small intestine is not dilated it may be assumed that the perforation is in the duodenum, and since there will be little danger of additional leakage, the stomach and duodenum having been deflated by the gastric tube, orderly exploration may proceed

2 The position of the colon is at once noted. If the cecum is not in its customary position on the right side of the abdomen or is not visible at all, malrotation is at once suspected. If a mass of bluish purple loops of small intestine present immediately, either collapsed or containing only a small amount of gas, volvulus about a common mesentery is more than likely. The obstruction may or may not be due to the malrotation, however

3 Distention of the stomach and duodenum alone implies that the point of obstruction is at or proximal to the ligament of Treitz

INTESTINAL OBSTRUCTION

4 Dilatation of the small intestine and a small, collapsed colon, indicates that atresia or stenosis in the small intestine is probable

5 Dilatation of the colon, as well as part of the small intestine, indicates a rare type of stenosis or atresia of the distal colon at or proximal to the sigmoid

The next step is evisceration and systematic exploration of the abdominal contents

Extrinsic duodenal obstruction The incompletely rotated colon is dealt with first. It is necessary to follow a deliberate and systematic course of procedure if confusion is to be avoided, for when the bowel is pulled this way and that in an attempt to find the point of obstruction rapidly it is far too easy for the operator to become confused and miss the true point of obstruction. The next step is to divide the hepatocolic ligament, free any lateral attachments to the cecum and the superior peritoneal attachments of the right half of the transverse colon which will usually overlie the transverse portion of the duodenum. This exposes the entire length of the duodenum to the ligament of Treitz and permits placing the entire colon on the left side of the abdomen. If the colon is in fetal position, never having rotated at all, and having formed no attachments on the right side, this step is unnecessary. If there is a volvulus of the entire small intestine which has rotated about the superior mesenteric artery, usually clock-wise, this is now replaced by untwisting the bowel and the mesentery until the latter is unobstructed and the jejunum follows a straight course from the ligament of Treitz (Figs 9, 10 and 11). The peritoneal attachments of the duodenum, laterally and inferiorly, are now freed up to and including the folds of peritoneum which comprise the ligament of Treitz, using great care not to injure the superior mesenteric artery which is carefully examined for abnormal bands or folds which may surround it. The duodeno-jejunal junction now lies to the right of the superior mesenteric artery and the duodenum empties vertically into the jejunum. One of the maneuvers just described will probably relieve the obstruction of the duodenum if it is due to the volvulus about the common mesentery, or abnormal attachments about the ligament of Treitz or the superior mesenteric artery. The exploration must not be discontinued at this point, however. The duodenum, which has been exposed, is carefully examined. If obstruction was present in the third portion of the duodenum, it will be elongated as well as dilated. The gastric tube or catheter is then passed through the duodenum into the jejunum. If it meets no obstruction, and passes readily into the jejunum, the operator may be assured that no obstruction remains up to that point. Gas is then followed through the entire small and large intestine to make certain of the patency of the remainder of the intestinal tract.

The procedure just described and illustrated was advocated by Ladd²¹ in 1932, and has been given credit for the striking improvement in cures of extrinsic obstruction of the duodenum.

Intrinsic duodenal obstruction If the stomach and duodenum remain dis-

tended and the catheter meets an obstruction in the second or third parts of the duodenum, the surgeon is faced with alternative possibilities (1) to do an anastomosis between the proximal duodenum and the jejunum or between

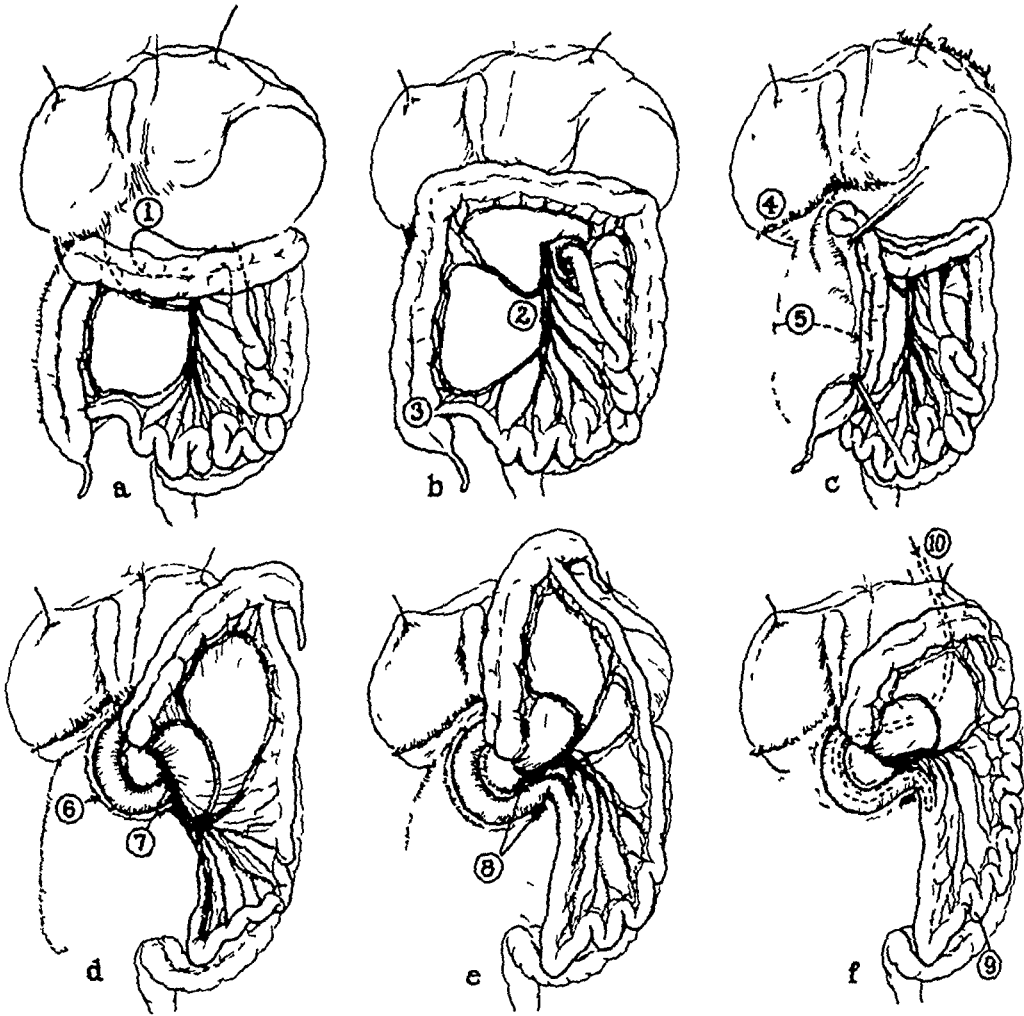


FIG 9—This series of diagrams represents the steps that we feel necessary for the complete exploration of the duodenum in order to properly evaluate the degree of obstruction that may be present. The operation must be done under adequate anesthesia and through an ample incision.

Step 1—Examination of the pylorus to rule out pyloric stenosis.

Step 2—Examination of the base of the mesentery.

Step 3—Examination of the cecum to determine the degree of rotation of the large intestine, to rule out volvulus of the small intestine.

Step 4—Cutting of the hepato-colic ligament to free the hepatic flexure of the colon.

Step 5—Cutting of the secondary attachments of the ascending colon to completely visualize the duodenum.

Steps 6 and 7—Cutting of the secondary attachments of the duodenum to the abdominal wall and the secondary attachments to the base of the mesentery of the small intestine at the superior mesenteric vessels. This does not interfere with the blood supply of the duodenum.

Step 8—Complete freeing of the secondary attachments of the duodenum at the ligament of Treitz to allow the duodenum to descend on the right side of the abdomen.

Step 9—Demonstration of the passage of gas into the small intestine.

Step 10—Passage of a Levine tube into the small intestine to rule out the presence of partial septa within the duodenum.

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the stomach and jejunum, or (2) to open the intestine at the point of obstruction in the hope of finding a leaflet which can be resected without anastomosis. If the stomach and proximal duodenum are markedly thinned out and lacking in tone due to distention of long standing, an anastomosis is probably the safer procedure since, even if the leaflet is removed, it will be a matter of days before the atonic stomach and duodenum are able to force fluid through the collapsed loops. If, however, the tone seems good and distention is not excessive, the procedure described by Morton²² and illustrated in Figures 9 and 10 may be useful. The bowel is incised longitudinally over the point of obstruction, and if a leaflet is found obstructing the lumen of the duodenum, it is resected, the mucosa carefully repaired, and the bowel wall closed in its transverse diameter. The catheter is then passed through the anastomosis.

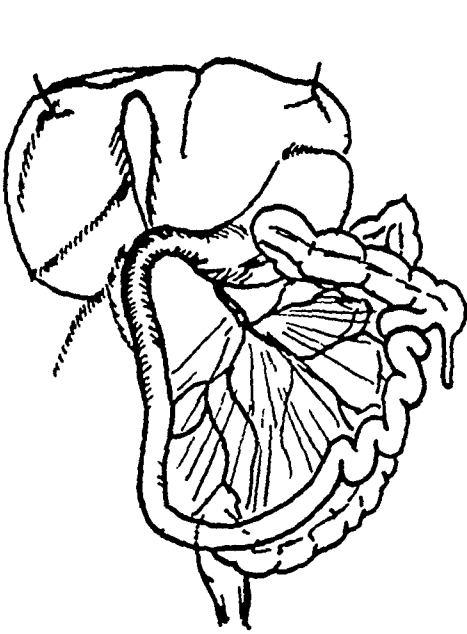


FIG 10

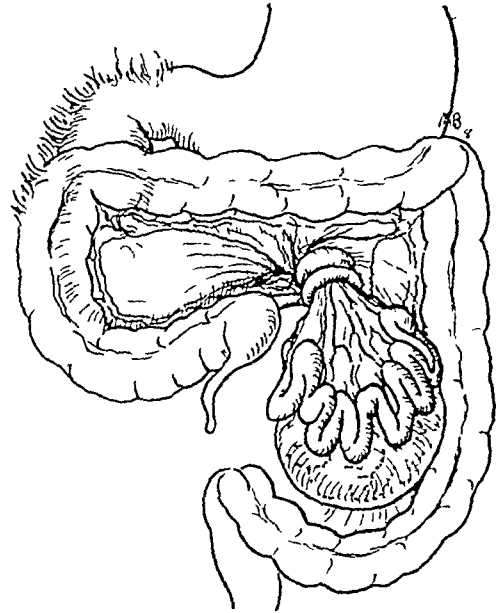


FIG 11

FIG 10—This is the final position in which the duodenum should be left, if possible, in all cases of malrotation of the colon with obstruction of the duodenum. With the duodenum descending on the right side of the abdomen and the colon on the left, the base of the mesentery is no longer a small point of fixation but becomes a wide base and postoperative recurrent volvulus should not occur.

FIG 11—Case 30—A complete 360 degree volvulus of the small intestine in a counter-clockwise direction was found. The case illustrates the fact that the duodenum may be dilated in this situation. It is not always. There was also herniation of a portion of the terminal ileum into its own mesentery, which is shown as a pouch that includes the volvulus. The colon was more completely rotated in this case than is usual in the presence of volvulus.

If, instead of the findings just described, there is obvious loss of continuity of the duodenum, either near the ampulla of Vater or near the duodeno-jejunal junction, an anastomosis is obviously the only choice. A duodeno-jejunostomy is generally preferred. If, however, the duodenum has been very

markedly distended, the wall thinned out, a gastro-jejunostomy through the thicker walled stomach may be somewhat safer. While a posterior anastomosis is preferable, an anterior anastomosis is perfectly satisfactory if it is easier to do. Our choice is for a lateral isoperistaltic duodeno-jejunostomy performed with two rows of 5-0 silk on atraumatic needles. No clamps are used, the thumbs and forefingers of the assistant serving as admirable holders which are much less traumatizing than clamps. The gastric catheter or Levine tube may now be passed through the anastomosis into the jejunum for a distance of 15 to 20 cm. to insure its patency, and the anesthetist may inject slowly, 5 or 10 ccs. of saline through the catheter into the jejunum. More saline may be introduced slowly through the catheter from time to time while the operation is being completed. This procedure aids in dilating and straightening out the loops of small bowel, helps the surgeon to be assured that continuity of the bowel exists, and at the same time provides the infant

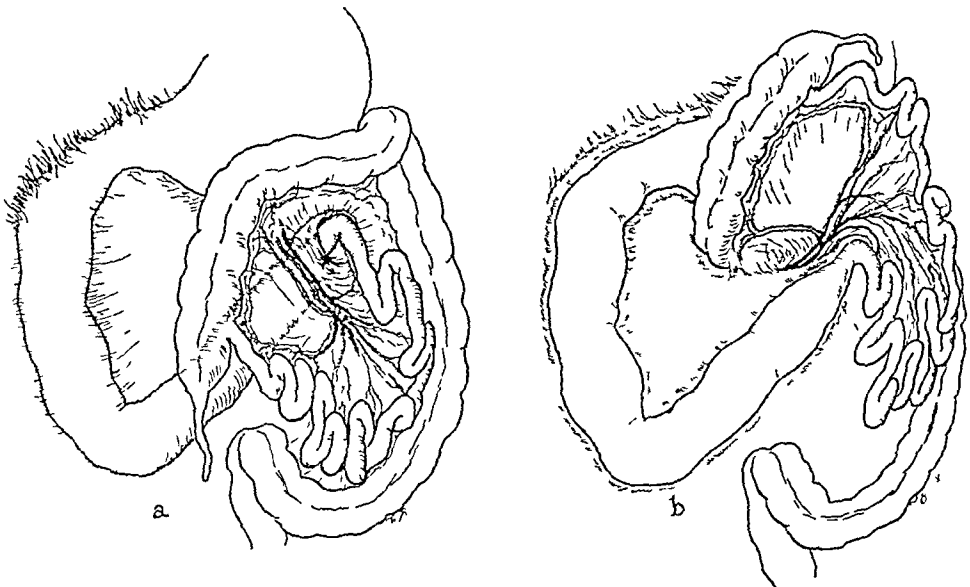


FIG 12—Case 34 (a) A typical instance of incomplete rotation and fixation of the colon with obstruction of the duodenum at the ligament of Treitz. Note the marked dilation and particularly the elongation of the duodenum which forces it completely out from under the colon. The surgeon often gains the impression upon first examination that the duodenum actually passes through the mesentery of the terminal ileum.

(b) By carefully dissecting the ascending colon free, it is possible to free the duodenum completely at the ligament of Treitz, by freeing the secondary attachments the duodenum can be brought down into the right lower abdomen, thus preventing recurrent postoperative volvulus by widening the base of the mesentery.

with badly needed electrolyte fluid. If there is a great discrepancy between the size of the duodenum and the collapsed jejunum, the latter may be dilated with saline prior to the anastomosis as an aid to suturing.²³ This is not usually necessary, however.

When obstructions of the duodenum have been relieved, especially those due to atresia of some days' standing, and where the muscle-tone of the former organs is lacking, it is absolutely essential to keep the stomach con-

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tinuously deflated in order to protect the integrity of the suture line of the anastomosis. It is also highly advantageous to be able to begin introducing feedings into the jejunum immediately after the operation. The presence of an indwelling catheter or tube is not well tolerated by the nasopharynx of the small infant, and favors aspiration. It is unsafe to leave the tube in place for more than a day or two continuously. The tube introduced through the nasopharynx does not, furthermore, serve effectively as a deflating mechanism, if it has been passed through into the jejunum, and if it is left in the stomach

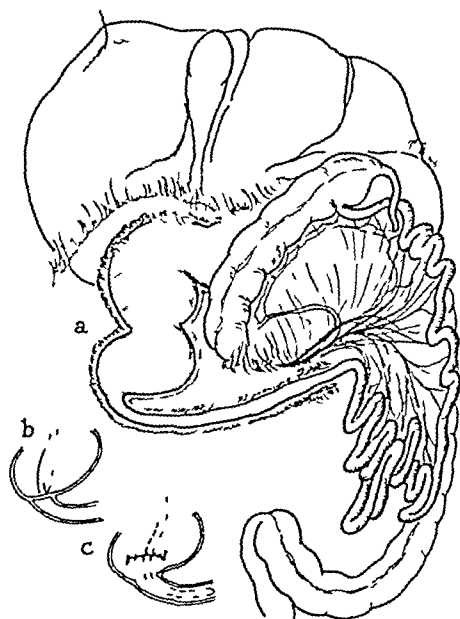


FIG 13

FIG 13—Case 10. A typical case of complete obstruction of the second part of the duodenum due to an imperforate septum. External adhesions were thought to be the cause of obstruction until it was discovered that the Levine tube would not pass, illustrating the importance of completing the steps of the exploration, as advised in the text.

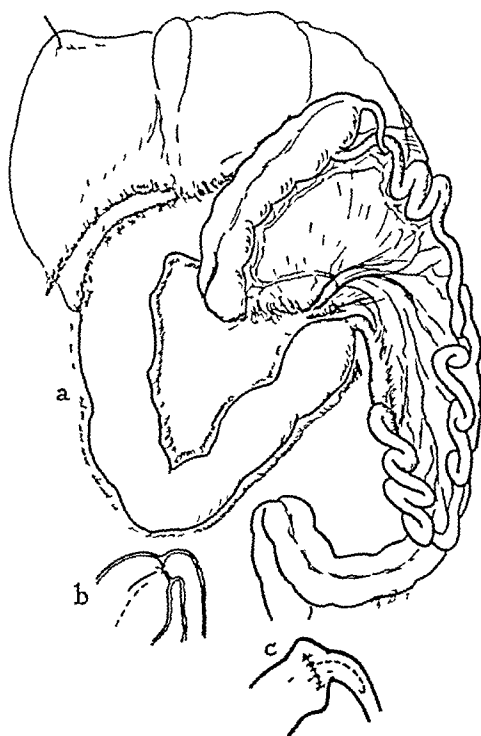


FIG 14

FIG 14—Case 11. The findings illustrate the not uncommon instance of two or more causes of duodenal obstruction in the same patient. Roentgenograms showed that the opaque material had passed the point of obstruction, which exploration proved to be at the ligament of Treitz. When an attempt was made to pass the Levine tube, a partial septum was found near the duodeno-jejunal junction. The use of a simple plastic procedure for removal of the septum, as shown in the illustration, is possible only if the duodenum is freed completely. Otherwise a duodeno-jejunostomy must be performed.

it is impossible to use it for feeding. The tragic results which may follow failure to keep the stomach deflated are illustrated by Case No. 3, where the anastomosis leaked.

The amount of air swallowed by the small infant during crying and gulping is astonishing. We have measured as much as 10 to 15 ccs of air swallowed per gulp while the baby was crying. It is easy to see that this amount will soon dilate the stomach and jejunum to a point where leakage at the anastomosis line is almost inevitable.

To overcome this objection we have introduced two small catheters through the stomach wall (Fig 16). The end of one catheter is passed through the anastomosis into the jejunum to serve as a feeding tube, while the other catheter remains in the stomach for maintaining continuous suction until the suture-line has had an opportunity to heal. The catheters are anchored securely to the stomach wall with fine silk sutures and also to the abdominal wall and are securely strapped to the abdominal wall with adhesive tape to avoid inadvertent removal. Through the feeding tube fluid can be introduced into the jejunum by slow drip, and within a day or so the infant's nutritional requirements can be met through this source.

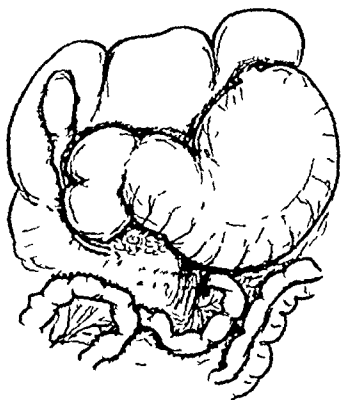


FIG 15

FIG 15—Case 3 Atresia of the duodenum proximal to the ampulla of Vater

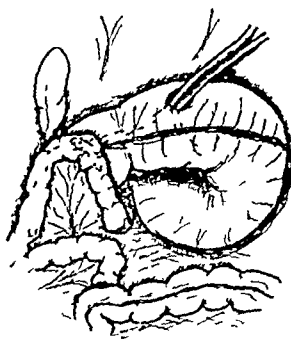


FIG 16

FIG 16—Case 3 A posterior duodeno-jejunostomy has been performed. Two small catheters have been placed through the gastric wall, one through the anastomosis to serve as a feeding tube and the other left in the stomach to aspirate swallowed air.

Final position of the colon While it has been asserted by Ladd that the colon must remain on the left side of the abdomen after the operation is completed in order to safeguard against subsequent intestinal obstruction, the senior author has on occasion deliberately placed the cecum and ascending colon on the right side of the abdomen, without any fixation whatever, and has left them in that final position. Roentgenogram (Fig 7) following barium enema six years after the operation on such a case shows the cecum and ascending colon to have remained in the normal position. It is interesting to note that gastro-intestinal series showed the duodeno-jejunal junction to have remained in vertical position on the right side of the abdomen, emptying in a perfectly normal manner. We have occasionally observed evidences that after birth the process of rotation of the colon, which was arrested during fetal life, may continue. This observation lends support to the procedure of leaving the colon in a position where it can continue rotation after birth and perhaps form normal attachments. This maneuver must be done with great caution, however, and if the bowel does not lie perfectly free over the small

intestine without twisting or kinking the mesentery, it is far safer to leave it on the left side in the fetal position

Other rare causes of obstruction which may be encountered are ring pancreas (Cases 1, 7), retroperitoneal hernia (Cases 31, 34), intramesenteric hernia (Case 30), and volvulus about remnants of the omphalo-mesenteric duct (Case 36)

Intrinsic obstruction of jejunum and ileum Since atresias of the small intestine are often multiple (Cases 15, 26) it is obviously most important to establish continuity with as much length of both small and large bowel as can be salvaged. Where the point of atresia or stenosis is single, a side-to-side anastomosis may be done quickly between the loops proximal and distal to the occlusion without disturbing the blind ends. If, however, the points of atresia are multiple it is usual to find a very short distal loop of ileum at the

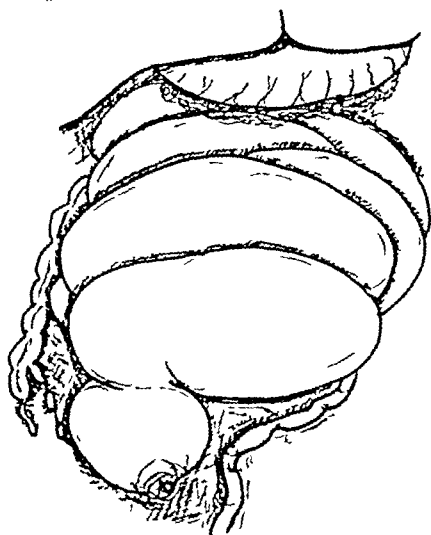


FIG 17



FIG 18

FIG 17—Case 17 Ileal atresia with perforation of the blind end of ileum. Two tiny segments of rudimentary intestine may be seen between the blind loop and the ileocecal valve.

FIG 18—Case 17 An end-to-side ileo-colostomy has been performed after resecting the distended blind loop and the rudimentary segments shown in Figure 17.

ileocecal valve and it is necessary to do an anastomosis between the markedly dilated proximal loop of ileum or jejunum and the colon, which is usually so small as to make the anastomosis difficult. Here an end-to-side anastomosis is probably best. A Witzel-type enterostomy tube should always be left in the dilated proximal loop to control distention until the anastomosis functions (Fig 18). Whether or not to leave the blind loops of ileum in place is a question that is usually determined by expediency. If they are so small as to be worthless they may as well be resected, if the procedure will not add unreasonable operative trauma. If the blind loop is of more than 20 cms length, however, it is well to leave it, on the chance that if the baby survives it may prove useful later. It is most important to make certain of the patency of the diminutive colon which is occasionally occluded by a cast-

like cord of cells (Case No 16) A useful expedient is to introduce the tip of the enterostomy catheter (before completing the Witzel closure) through the anastomosis into the colon, and through this to introduce saline which can be milked along the colon to insure its patency and continuity The colon may also be dilated from below by repeatedly introducing fluid through the rectum

It is sometimes tempting to do an anastomosis between the dilated ileum and the sigmoid colon which looks slightly larger in calibre than the diminutive ascending and transverse colon (Case 17) but this should not be done because it permits the baby to lose fluid too rapidly to get ahead Open ileostomies are to be condemned The surgeon should use every possible effort to do a definitive operation that will make it possible for the infant to acquire his nutritional requirements through the intestinal tract at the earliest possible date The time required to do an anastomosis is insignificant if the baby is receiving blood during the operation

When the entire large bowel down to the descending colon or sigmoid is found to be enormously dilated, as well as part of the ileum, the point of obstruction will usually be found in the lower colon, but it may not be complete and the findings may be confusing (see Case No 20) In such cases a catheter usually can be introduced through the rectum and fed through the narrow point unless the obstruction is complete enough to require resection and immediate anastomosis In either case, a temporary tube cecostomy is worth-while to decompress the bowel until the stenotic area can be dilated

Atresia of the rectum Atresia of the rectum is usually readily diagnosed by the lack of an anal opening, failure to obtain meconium by probing the intact anal plate, and by plain roentgenograms taken in the head down position as suggested by Wangenstein²⁴ The latter procedure forces gas in the blind end of the colon in the pelvis, usually near the bladder neck, where it can be easily seen With this evidence, operation should always be performed through the perineum By very careful, gentle dissection through a small incision, the blind end of bowel can usually be found in the region of the bladder neck and can be freed retroperitoneally, sufficiently to mobilize it and bring it down to the perineum The bowel is opened and sutured to the skin, the sphincter being reconstructed at the same time These procedures are highly successful and carry a very low mortality Abdominal colostomy is almost never necessary in such cases and should be avoided

CASE REPORTS, INTRINSIC OBSTRUCTION

Case 1—The infant was born with several anomalies and was not operated upon At autopsy complete atresia of the duodenum was found proximal to the ampulla of Vater (Previously reported²⁵)

Case 2—A premature male infant weighing 3 pounds and 8 ounces was explored on the fourth day of life Markedly distended stomach and duodenum were found The patient stopped breathing several times during the procedure, which was terminated without attempt to relieve the obstruction The baby died two days later Autopsy showed incomplete stenosis of the second part of the duodenum and a perforated ulcer of the ileum A patent ductus arteriosus and a patent foramen ovale were also present

Case 3—A male premature infant weighing 5 pounds was observed to vomit all feedings from the time of birth, the vomitus resembling meconium. A small amount of meconium was also passed per rectum. The vomitus contained no bile. When seen 24 hours after birth, the infant's abdomen was tensely distended throughout, liver dullness was obliterated and the skin was shiny, with mottling and venous engorgement. Plain roentgenograms showed marked distention of the stomach and proximal duodenum with no gas visible elsewhere in the intestinal tract. A large amount of free air was present in the peritoneum (Fig. 2). At operation 36 hours after birth atresia of the duodenum proximal to the ampulla of Vater was demonstrated. The cecum was in fetal position on the left side of the abdomen. The perforation could not be identified since the stomach and duodenum had been evacuated through a No. 10 catheter passed into the stomach, but was assumed to be in the first part of the duodenum where distention had thinned the wall greatly. An isoperistaltic duodeno-jejunostomy was performed with 5-0 silk in three layers, and the catheter was passed through the stoma into the distal limb of the jejunum for feeding purposes. The baby was given whole blood followed by Ringer's solution by bone marrow infusion during and after the operation. The baby's condition was excellent the following day and small feedings were begun through the tube. On the second day he passed several milk stools mixed with meconium. It was necessary to place an additional catheter in the stomach to decompress the air the baby swallowed constantly. On the fifth day it was apparent that the baby again had pneumoperitoneum. Assuming that the anastomosis had leaked, the incision was reopened and that fact confirmed. The anastomosis was repaired and two small catheters were introduced through the stomach wall, one going through the anastomosis to serve as a feeding tube and the other to keep the stomach decompressed. The baby died the next day apparently of shock and bile peritonitis.

Case 4—The full term infant began vomiting soon after birth, but retained part of its feedings, and during this admission evidence of obstruction was unrecognized. At ten months of age he was readmitted with a history of intermittent vomiting since birth and failure to gain weight, and died within a few minutes of admission. Autopsy showed incomplete stenosis due to a leaflet in the second part of the duodenum proximal to the ampulla. (Previously reported²⁵)

Case 5—The infant was operated on at six days of age and lysis of adhesions performed in the region of the ampulla where obstruction seemed to exist. The baby died eight days later from what was presumed to have been an intrinsic stenotic lesion just distal to the ampulla. (Previously reported²⁵)

Case 6—A 2½-pound premature female infant whose vomiting from the time of birth was projectile and bile-stained was admitted about eight hours after birth. Marked visible peristalsis was noted from left to right in the upper abdomen and the roentgenogram showed a typical picture of duodenal obstruction. Under local anesthesia and with bone marrow transfusion running, exploration showed the infant to have a ring pancreas. After dividing the encircling ring of pancreas, however, it was found that a catheter could not be passed through the duodenum at this point due to complete stenosis. A duodeno-jejunostomy was accordingly performed and the catheter passed through the anastomosis. The baby passed milk stool on the second day but succumbed on the fourth day.

Case 7—A five-weeks'-old infant was admitted with a history of vomiting bile-stained material intermittently and increasingly in amount, weight loss and dehydration. There was marked visible peristalsis, and roentgenograms showed dilatation of the stomach and proximal duodenum. Exploration showed a ring pancreas to be the apparent cause of obstruction. This was divided. Because of continued vomiting the baby was reoperated upon four days later. Since it was apparent that an intrinsic stenosis existed distal to

the ampulla, an anterior gastro-jejunostomy was performed. The baby recovered without incident and has remained well for 12 years (Previously reported ²⁵)

Case 8—The newborn infant was observed for ten days prior to death, but not operated upon. In spite of the fact that roentgenograms had showed that barium passed freely into the small intestine, at autopsy esophagus, stomach and duodenum were enormously distended due to intrinsic stenosis at the duodeno-jejunal junction (Previously reported ²⁵)

Case 9—A six-weeks'-old infant was explored for pyloric stenosis which was not found. At autopsy a few days later partial stenosis at the duodeno-jejunal junction was demonstrated. The infant also had other anomalies (Previously reported ²⁵)

Case 10—A female infant was admitted two days following delivery, with a history of vomiting bile-stained material on the first day. On the second day of life the vomitus contained coffee ground material. The stool contained only meconium. Examination showed the upper abdomen to be distended after feedings, with peristaltic waves running from left to right, and flat roentgenograms showed the gas-filled stomach and duodenum. Upon exploration, rotation of the colon was found to be complete. The first and second part of the duodenum were dilated and elongated. The transverse portion of the duodenum was normal and the Levine tube would not pass into this portion (Fig 13). The duodenum was opened longitudinally across the point of constriction and a complete septum was found at that point. The septum was excised and the incision was closed transversely. Recovery was uneventful and the child has remained in normal health for seven years.

Case 11—A ten-day-old infant was admitted with a history of intermittent vomiting since birth, but for the few days prior to admission all of each feeding was vomited, and the vomitus contained bile but no blood. Stools were scanty but normal in color. Examination showed upper abdominal distention after feedings, with visible peristalsis. Roentgenograms with barium showed an enlarged and elongated duodenum with almost complete obstruction at the ligament of Treitz. Very small amounts of air and barium passed into the small intestine. Three days after admission the abdomen was explored. The duodenum was tremendously enlarged and elongated. At the ligament of Treitz were a kink and a band which were freed but the Levine tube still failed to pass that point. The duodenum was opened at that point and a septum was found, in the center of which was a slit-like valvular opening 4 mm in length (Fig 14). The septum was excised and the incision in the bowel was closed transversely. Roentgenograms 17 days later showed marked improvement but not return to normal. The patient has remained well for two years since operation.

Case 12—The patient was operated upon on the day of birth. The distal 2 feet of ileum were represented by a small band about which was twisted the blind end of ileum, the latter being gangrenous. An ileostomy was done and the baby died 24 hours later (Previously reported ²⁵)

Case 13—This baby presented a picture similar to Case No. 12 when operated upon on his third day of life, and he died following ileostomy (Previously reported ²⁵)

Case 14—This female infant, explored on the first day of life, was found to have a stenosis of the distal ileum with marked dilatation of the proximal ileum and jejunum. A resection and side-to-side anastomosis was performed. Vomiting and abdominal distention continued intermittently and when two weeks later the abdomen was reexplored a supplementary lateral anastomosis was performed between the proximal ileum which still remained dilated and the ascending colon. Her condition was improved following this procedure but she did not gain well, and had intermittent bouts of abdominal distention suggesting partial obstruction. In spite of adequate supportive therapy she developed pneumonia and died four weeks after the initial operation. Autopsy showed no other

evidence of intestinal anomaly, but the baby had a patent ductus arteriosus and a patent septal defect

Case 15—A female infant weighing approximately 5 pounds was admitted 48 hours after birth with a history of vomiting all feedings, with marked distention of the upper abdomen, visible peristalsis and roentgenographic evidence of marked distention of the stomach and entire duodenum. A side-to-side anastomosis was performed between the third part of the duodenum and the distal ileum. In spite of supportive therapy the infant died the following day. Autopsy showed seven points of atresia between the ligament of Treitz and the ileocecal valve (Previously reported in detail²⁶)

Case 16—This male infant was admitted to the hospital eight days after birth with a history of vomiting intermittently since birth and only one meconium stool passed on the fourth day of life. In spite of the vomiting the infant had taken feedings well. At first the vomitus was bile-stained but subsequently became fecal in character. An enema on the day of admission brought returns of greenish mucus. Roentgenograms showed a typical picture of obstruction of the distal ileum. At operation upon the day after admission, atresia was found in the distal ileum, with marked dilatation of the entire intestine proximal to the point of obstruction. An end-to-end ileostomy was performed after resecting the dilated distal loop and distending the distal ileum with saline to increase its size. On the seventh postoperative day the anastomosis perforated and the baby died of peritonitis. Terminally the infant was edematous, probably due to administration of an excess amount of parenteral fluid. Autopsy showed the distal loop of ileum and the ascending colon to be almost occluded by a cord-like mass of cellular debris which had prevented the functioning of the anastomosis. Patient also had patent ductus arteriosus, patent foramen ovale and portal thrombosis.

Case 17—A premature female infant seen on the third day of life had begun vomiting on the first day and on the day prior to examination had vomited all feedings. The vomitus contained bile. The abdomen was uniformly distended, with drum-like tympany throughout, the skin being stretched so that the superficial veins were easily visible. Liver dullness was obliterated. Baby had passed a little meconium on the first day but nothing subsequently. Roentgenograms showed enormous distention of several loops of small intestine as well as free fluid and gas in the peritoneal cavity (Fig. 3). Operation was performed on the third day of life, under local anesthesia, through a lower transverse incision while blood was given via bone marrow. The peritoneal cavity contained a large amount of free gas and a moderate amount of greenish fluid. It was found that the enormously distended ileum ended in a blind loop which was fixed in the pelvis and had perforated, and that there were two tiny segments of rudimentary bowel about 1 cm. by 4 mm. in diameter between this point and the ileocecal valve (Fig. 17). Colon was in normal position but only about 5 mm. in diameter. The distended distal ileum had twisted upon itself in such a manner as to produce virtually a closed loop approximately 4 cm. in diameter by 10 cm. in length. This loop contained thick liquid material and gas and the wall was almost gangrenous. This loop was resected and a lateral anastomosis was performed between the ileum and the sigmoid colon, which seemed to be the only part of the colon large enough to be likely to function effectively, and an ileostomy tube was placed in the distal end of the ileum. The infant took feedings well, passed stools from the rectum immediately following the operation and fluid balance was maintained by parenteral electrolyte solution and intramarrow transfusions of whole blood and plasma. Frequent stools continued from the rectum but drainage from the ileostomy gradually increased in amount until at the end of three weeks it was apparent that the patient was losing fluid more rapidly than could be compensated for. Accordingly, at this time the ileostomy was resected and an end-to-side anastomosis was performed between the distal ileum and the ascending colon which had now increased in size until it was about 1 cm. in diameter. After this procedure the infant began to improve rapidly but still required some parenteral

feedings. She died suddenly following an intramarrow plasma infusion at the age of four weeks. While fat embolus from too rapid introduction of the plasma was suspected as the cause of death, this could not be confirmed at autopsy. No other anomalies were disclosed.

Case 18—This male infant of 5 pounds, 14 ounces at birth, began vomiting immediately after birth and was suspected of having an intracranial lesion for the first three days. It was apparent on the third day, however, that the baby had a complete intestinal obstruction. Operation was performed on the fourth day disclosing an atresia of the distal ileum and a lateral ileo-transverse colostomy was performed. The baby was in poor condition at the time of the operation and the anastomosis never functioned. He died on the first postoperative day. No autopsy was obtained, but there seems to be some question if the colon was actually patent distal to the anastomosis in this case.

Case 19—This infant was operated upon the third day of life, presenting an atresia of the entire colon down to the distal sigmoid. The baby died following ileosigmoidostomy (Previously reported ²⁵).

Case 20—This male infant of normal size began to show abdominal distention soon after birth and on the third day began to vomit. Roentgenograms (Fig 6) showed marked distention of all intestinal loops and barium introduced per rectum showed marked distention of the entire colon down to the sigmoid. At operation, performed on the fourth day of life, no point of obstruction was found. Autopsy performed 24 hours later showed incomplete stenosis to exist in the midportion of the sigmoid colon. Patient also had a patent ductus arteriosus and a patent foramen ovale.

Case 21—This 18-hour-old term female infant showed abdominal distention from birth, vomited bile and passed no stool. Roentgen examination showed marked distention of the stomach and duodenum and what was interpreted as gas in the colon, thought to be due to an enema. She was transfused and operated upon under drop ether anesthesia and found to have an atresia of the terminal ileum with a wedge shape defect in the mesentery and a collapsed portion of ileum below that point. A lateral anastomosis between the dilated and collapsed loops of ileum was done, and the child recovered. She was later admitted with a diagnosis of fibrocystic disease of the pancreas. She is the sibling of Case 46 who had a meconium ileus and fibrocystic disease of the pancreas.

Case 22—This one-day-old term female infant was operated upon on the first day of life under drop ether anesthesia because of abdominal distention and absence of stool. Roentgenograms showed dilatation of the greater portion of the small intestines. There was found to be complete atresia of the terminal portion of the ileum, a wedge shaped defect in the mesentery and a collapsed distal loop of ileum. A lateral anastomosis was performed between the distal and proximal loops, but the child died after eight hours.

Case 23—This one-day-old term male infant vomited and became distended from the time of birth, and the vomitus contained bile. Roentgen examination showed dilatation of the greater portion of the small intestine. He was transfused and explored under drop ether anesthesia and found to have a complete atresia of the terminal ileum with a wedge-shaped defect in the mesentery. An end-to-end ileo-cecostomy was done, with survival.

Case 24—This two-day-old term male infant was seen because of vomiting of bile and distention of the abdomen since birth and a roentgenogram showing dilatation of the greater portion of the small intestines. He had a complete situs inversus. He was transfused and explored under drop ether anesthesia and found to have an abdominal situs inversus with the exception of the large intestines. There was a reverse rotation of the colon so that the duodenum which was on the left side descended directly into the jejunum and was not retroperitoneal at all. The colon lay with the cecum in the right lower quadrant but it passed up and behind the small intestines instead of in front of it and was a retroperitoneal organ. There was a complete defect in the terminal ileum, with

several small cystic remnants of ileum in the terminal portion and a collapsed terminal ileum about three inches in length. An ileo-cecostomy was performed. This functioned postoperatively, but only poorly, because there was a continuing partial obstruction in the colon where it passed behind the superior mesenteric vessels and the dilated jejunum. An ileostomy was done above the anastomosis 11 days after the original operation in an attempt to decompress it, but in spite of this the child died 27 days later. In retrospect it would seem that something should have been done to prevent the obstruction in the transverse colon, either by doing the anastomosis to the left half of the transverse colon, or of transecting the colon and reanastomosing it in front of the vessels.

Case 25—This three-day-old term female infant was noted to refuse all feedings from birth, and to vomit bile. The abdomen became distended and peristalsis was visible. No roentgen examination was made. She was transfused and operated upon under drop ether anesthesia and found to have a diaphragm across the terminal ileum 8 inches above the ileocecal valve. A plastic operation was done on the valve, excising it and closing the gut. At the time of the operation it was felt that there was some question about the viability of the intestines adjacent to the septum. The child died after 8 hours, from peritonitis. Postmortem examination also showed incomplete expansion of the lungs.

Case 26—This three-day-old term male infant was noted to have had no stools and to vomit, the vomitus containing bile. A barium enema was done, and the colon filled only to the splenic flexure and there was tremendous dilatation of the small intestines. The child was transfused and operated upon under drop ether anesthesia. There was a focal area of marked enlargement of the jejunum and multiple areas distal to that in the ileum and colon in which there was no apparent lumen of the intestines. Interposed were segments of apparently normal intestine. These were interpreted as multiple areas of complete atresia and nothing was done. The child died after six days and at autopsy the area of dilated jejunum previously described was again noted, and although the remaining portion of the intestinal tract had a lumen it was reduced in size. The apparent cause of death was peritonitis.

CASE REPORTS, EXTRINSIC OBSTRUCTIONS

Case 27—This five-day-old infant had vomited bile or bile-stained fluid since birth. Examination revealed distention and visible peristalsis in the upper abdomen, stools were brown and soft with curds. Roentgenograms with opaque material revealed the stomach and duodenum to be widely dilated, and what little opaque material entered the jejunum was on the right side of the abdomen. A few gas shadows on the left suggested colon. The history and roentgen findings were considered typical of partial duodenal obstruction due to malrotation and volvulus. At operation, the cecum was found to be in the upper abdomen overlying the duodenum and there was a 360 degree clockwise volvulus of the entire small intestine. There was also partial obstruction of the first part of the jejunum where it went through a defect in the mesentery, and it was further fixed by the peritoneal attachments of the cecum. The latter were freed, and the volvulus reduced. The attachments of the duodenum were not freed. Recovery was uneventful, and the patient has remained well for ten years. (Previously reported²⁵)

Case 28—A five-weeks'-old infant presented a picture of high intestinal obstruction and upon exploration disclosed a partially rotated colon with stenosis of the second part of the duodenum due to the peritoneal attachments of the unrotated cecum. Freeing these permitted filling of the third part of the duodenum and jejunum. The attachments of the duodenum and cecum were not otherwise disturbed. The baby's recovery was uneventful. (Previously reported²⁵)

Case 29—A healthy appearing infant of almost 8 pounds at birth, began vomiting the first day after birth and continued to vomit with increasing frequency until seen by

the pediatrician and surgeon on the seventh day. The vomitus contained bile. The baby passed meconium on the first day, a few small yellow or brown stools on the second and fifth days, and had no stools on the sixth and seventh days. When seen he was dehydrated and showed upper abdominal distention with marked visible peristalsis. Roentgenograms taken following ingestion of barium showed marked dilatation of the stomach and duodenum and only a few flecks of barium in the small intestine. Barium injected by rectum showed the colon to be entirely on the left side (Fig 7). The diagnosis of malrotation with volvulus was confirmed at operation. Reduction of the volvulus did not relieve the duodenal obstruction, however, because it was constricted near the ligament of Treitz by peritoneal bands. Release of the attachments of the cecum and transverse colon and duodenum permitted the duodenum to empty freely. Without disturbing the root of the mesentery, the cecum was carefully rotated to the right lower quadrant of the abdomen and left there without fixation. Recovery was uneventful. The child has remained free from symptoms for eight years. Roentgenograms following barium enema taken six years after operation showed the entire colon to occupy the normal position (Fig 7). The duodenum emptied vertically into the jejunum on the right side of the abdomen.

Case 30—E W, a 2900 Gm premature male infant had been in the hospital since birth. Although his development had been slow, he seemed to be progressing normally except for intermittent vomiting. On the 40th day following delivery, he began to vomit everything that he took by mouth. The vomitus occasionally contained blood. Physical examination revealed an underdeveloped and dehydrated infant. The upper abdomen was distended and there were visible peristaltic waves passing from left to right across the upper abdomen. Roentgenological examination revealed a gas bubble in the stomach and another in the duodenum, and a uniform ground-glass appearance of the lower abdomen. The child was transfused and explored through a right rectus incision under drop ether anesthesia. On examination of the ligament of Treitz, there was found to be a complete 360 degree volvulus of the entire small intestine in a counter clockwise direction. The cecum was completely rotated, but the distal ileum disappeared through what appeared to be the orifice of an internal hernia. As the volvulus was reduced, it was found to completely obstruct the duodenum at the ligament of Treitz. The duodenum proximal to that point was elongated and dilated. As the mesentery was straightened out, there was found to be a secondary obstruction due to the herniation of the terminal ileum into a sac formed by an outpocketing of a fold of mesentery between two vascular arcades. About 8 inches of intestine were in this sac (Fig 11). The hernia was reduced, and the sac obliterated by suturing its mouth. The colon was mobilized, the duodenum completely freed and explored, and a tube passed through it. The colon was allowed to fall back to the left side of the abdomen and was not reattached. The child's postoperative course was uneventful and he was discharged 2 weeks later. The patient was readmitted 2 weeks later with another bout of intestinal obstruction. He was explored and secondary adhesions in the terminal ileum were found to be the cause of obstruction. His recovery was uneventful.

Case 31—B W, a four-day-old colored boy was admitted to Babies' and Children's Hospital following a normal delivery with a history of vomiting almost all feedings since birth. Vomiting followed feedings by 20 to 30 minutes and the vomitus contained bile. The stools contained meconium, and on one occasion appeared normal. Roentgenologic examination revealed dilatation of the stomach, air in the duodenum, and almost none in the small intestine. The child was explored under drop ether anesthesia on the fourth day of life. The cecum was found in the right upper quadrant. The first, second and third portions of the duodenum were enlarged. On examination of the ligament of Treitz, a herniation of the first part of the jejunum into a retroperitoneal sac adjacent to the ligament of Treitz was found. This was the cause of obstruction, and when it was reduced, air passed freely. The sac was obliterated and the

abdominal wall closed, leaving the intestine in place. The child did not do well, and continued to vomit. Repeated roentgenologic examination showed that some gas passed into the small bowel, but very little. On the sixth postoperative day, the child was explored a second time. The neck of the previous hernia was closed, but there was a complete 270 degree volvulus of the entire small intestine with the ligament of Treitz and colon as an axis. The volvulus was reduced, and the hepatocolic ligament divided. The lateral peritoneal reflection of the right colon was incised, and the duodenum completely freed and explored with a Levine tube. The colon was allowed to drop back into the left side of the abdominal cavity. The child's recovery was complicated by continued vomiting of parts of each feeding for several weeks. The child continued to lose weight for 6 weeks, but at that time vomiting diminished, and he began to gain weight. His eventual recovery was complete.

Case 32—The newborn infant was observed for eight days while vomiting and distention increased. At operative exploration the entire small intestine and the large intestine up to the splenic flexure were described by the operator as dilated. No error of rotation was noted. The baby died following ileostomy and no autopsy was obtained. It seems possible that this was a case of reversed rotation. (Previously reported²⁵)

Case 33—The newborn infant was operated upon with a diagnosis of pyloric stenosis, but obstruction was found to be due to a defect in the gastro-colic omentum through which a loop of jejunum had herniated into the omental bursa. Recovery followed replacement of the bowel and closure of the defect. (Previously reported²³)

Case 34—J. P., a seven-day-old white girl was born October 19, 1947, following a normal pregnancy and spontaneous delivery. She was fed within 12 hours, and vomited immediately. She was offered several formulae, but never retained more than half of a 30 cc feeding. On the day before admission, she vomited everything despite atropinization to the limit of tolerance. The infant had been maintained on parenteral fluids. Physical examination revealed a normal, healthy female infant. Following each feeding the upper abdomen was greatly distended with fluid and air, and peristaltic waves were visible passing from left to right. Vomiting was immediate and projectile, the vomitus contained bile. The stools were meager and light brown. Roentgenologic examination on October 23, 1947, revealed a large amount of air in the stomach and duodenum, and a moderate amount in the small intestine. Barium studies showed an obstruction in the third portion of the duodenum beyond which only very small flecks of barium passed. Under drop ether anesthesia, the duodenum was explored. The rotation and fixation of the intestine were normal. The first and second portions of the duodenum were dilated and elongated. On freeing the third portion of the duodenum, the superior mesenteric artery was found in a tight fold of peritoneum which constricted the portion of duodenum which passed beneath it (Fig 12). The entire duodenum and colon were mobilized. Postoperatively the child was fed 5 per cent Karo within 12 hours, and protein SMA after 24 hours. She continued to vomit small amounts of some feedings in decreasing amounts for 6 days, although the vomiting was never projectile and peristaltic waves were never visible. After the first week recovery was uneventful.

Case 35—R. V., a five-day-old white girl was admitted to the Babies' and Children's Hospital with a history of vomiting all feedings since birth, in spite of dietary modifications and atropinization. Pregnancy was normal and delivery by low forceps uncomplicated. She vomited the first and subsequent feedings completely. The vomitus contained bile, and after 48 hours flecks of blood. The stools were scant but contained bile. Physical examination was normal. Roentgenologic examination revealed air in the stomach, first and second portions of the duodenum and a small amount of air in

the small intestine Injection of 60 cc of air through the Levine tube into the stomach accentuated the radiographic picture The child was explored on the fifth day of life under drop ether anesthesia The intestines were normally rotated The proximal duodenum was dilated and elongated up to the ligament of Treitz, where there was a definitely tight peritoneal band When this was freed, gas passed freely into the jejunum and a Levine tube passed easily The child's convalescence was slow She continued to vomit 5 to 10 cc of each 60 cc feeding for ten days At the time of discharge, vomiting had ceased and the stools were normal

Case 36—This ten-week-old normal term male infant developed severe vomiting and progressive abdominal distention, and was admitted to the hospital 40 hours after the onset of symptoms He was severely dehydrated The abdomen was quiet Roentgen examination showed dilatation of the entire small intestine with a typical ladder pattern After blood and electrolyte balance were restored, his abdomen was explored under drop ether anesthesia A Meckel's diverticulum existed with a cord extending from its tip to the ileo-cecal valve and the intervening gut was caught under this cord, twisted and gangrenous The gangrenous segment was resected and an ileo-cecostomy done, with survival

Case 37—This six-day-old term male infant vomited most of his feedings from birth The vomitus contained bile and the stools were scant Roentgenograms showed distention of the stomach and duodenum and barium studies showed partial retention of barium in the stomach after 24 hours He was transfused and the abdomen explored under drop ether anesthesia An incomplete attachment of the colon with a 360° clockwise volvulus of the entire small intestine on the ligament of Treitz was found The volvulus was reduced, the duodenum freed and left on the right side of the abdomen, and the colon on the left The child recovered and had no further vomiting

Case 38—This two-day-old premature male infant was seen because of persistent vomiting of bile-stained material, no stools, and distention of the upper abdomen Roentgenograms showed a dilated stomach and duodenum, and no air in the rest of the intestinal tract He was transfused and operated upon under drop ether anesthesia and found to have incomplete rotation and fixation of the colon with a 360° volvulus, counterclockwise, of the entire small intestine This was reduced and the duodenum completely freed and returned to the right side of the abdomen, the colon to the left The child had some vomiting postoperatively for ten days Since then the child has developed normally

Case 39—This 18-day-old term male infant's abdomen was explored under drop ether anesthesia after 15 days of conservative treatment for persistent vomiting of bile-stained material, upper abdominal distention, visible peristalsis and scanty stools He was found to have a 360° volvulus of the entire small intestine at the ligament of Treitz with incomplete obstruction of the duodenum The volvulus was reduced and nothing else done The child survived and developed normally

Case 40—This three-day-old, six weeks premature, male infant had vomited bile-stained material since birth Roentgen examination showed some air in the intestinal tract and a suggestion of fluid between the loops of intestine, indicative of peritonitis He was operated upon under drop ether anesthesia and found to have an incomplete rotation of the colon with a 720° counterclockwise volvulus of the entire small intestine The small intestine was gangrenous so that nothing could be done, and the child died in three hours

Case 41—This three-day-old term male infant was admitted because of vomiting of bile-stained material since birth Roentgenograms showed a dilated stomach and

duodenum and absence of air in the small intestines. Exploration done under drop ether anesthesia showed an obstruction at the ligament of Treitz, presumably due to extrinsic bands, but the duodenum was not freed. A duodeno-jejunostomy was done and the child survived and developed normally.

Case 42—This two-and-one-half-months-old female infant was admitted because of failure to gain weight, vomiting of bile-stained material, visible peristalsis from left to right in the upper abdomen and barium retention in the stomach after six hours. She was operated upon under drop ether anesthesia and found to have an enlarged stomach and duodenum with obstruction that was interpreted as extrinsic at the ligament of Treitz. A duodeno-jejunostomy was done and the child died of peritonitis on the fifth postoperative day. Autopsy demonstrated a partial stenosis in addition to the extrinsic fold, which caused partial obstruction at the duodeno-jejunal junction.

Case 43—This six-week-old premature male Mongolian idiot had had vomiting of bile-stained material since birth. The upper abdomen was distended and the stool scanty. Roentgen-ray examination showed tremendous dilatation of the stomach and duodenum and no air in the small intestine. He was operated upon under local anesthesia and found to have an incomplete rotation of the colon with obstruction of the duodenum at the ligament of Treitz due to extrinsic peritoneal folds. These were freed and the child was better for 2 days but again began to vomit, and died on the sixth postoperative day. Autopsy showed, in addition to the extrinsic obstruction, a partial septum at the ampulla of Vater.

Case 44—This six-day-old female term infant had had jaundice since birth and vomited all feedings, the vomitus containing bile. There was visible distention of the upper abdomen and peristalsis from left to right. Stools were absent. She was operated upon and found to have extrinsic obstruction around the second portion of the duodenum due to bands, which were freed. The patient died 13 days postoperatively. Autopsy revealed, in addition to the extrinsic obstruction, a partial septum at the ampulla of Vater.

Case 45—This three-day-old term male infant vomited bile and all feedings from birth. The upper abdomen was distended and he had no stools. Roentgenograms showed a tremendous double loop of duodenum and a small stomach. He was operated upon and an extrinsic obstruction at the ligament of Treitz, incised freeing the duodenum. He did not improve and on his tenth postoperative day was reoperated upon and the duodenum was freed more completely. He continued to vomit, and died six days later. The surgeon interpreted this case as one of primary megaloduodenum.

Case 46—This two-day-old term female infant was admitted because of distention of the abdomen and small stools containing only meconium. Roentgenograms showed distention of the small intestines. She was operated on under drop ether anesthesia and found to have two areas in the small intestines in which the gut was herniated into its own mesentery, requiring a double resection of the small intestine and lateral anastomosis. The child died after five days, of peritonitis.

Case 47—This one-day-old term male infant vomited bile from birth and showed marked abdominal distention. Roentgen examination showed distention of the entire small intestine, the stomach and duodenum. He was operated upon under drop ether anesthesia and the jejunum and a portion of the ileum were markedly dilated. Beginning in the mid-portion of the ileum there was an abrupt diminution in the size of the gut to a cord like structure which contained inspissated meconium. This was broken up and partially passed into the colon by massage and the injection of saline through a fine needle. On the operating table the child had two large meconium stools. He died 24 hours later. The autopsy showed that the lumen of the intestines was patent but that the abrupt change in the size of the gut persisted. The child also had fibrocystic disease of the pancreas.

COMMENT

The small series of cases reported does not lend itself to complete statistical analysis. The figures presented in the tables may, however, justify certain generalizations. It seems apparent that the extrinsic obstructions represented by errors of rotation, carry a distinctly lower mortality rate than do the intrinsic defects, chiefly because they are incomplete. The atresias carry a much higher mortality rate because they represent complete obstructions, and also because they are frequently accompanied by associated anomalies, chiefly cardiac.

TABLE I—*Mortality*

Type of Obstruction	Authors' Series		
	Cases	Deaths	Mortality
Extrinsic	16	4	25%
Extrinsic and intrinsic	4	3	75%
Intrinsic	24	18	75%
Totals	44	25	57%
Ladd's Series ²¹			
Extrinsic	59	22	37%
Intrinsic	87	64	73%
Totals	146	86	59%

In this report we have not attempted to separate the intestinal atresias from the stenoses, since the classification is difficult at best, and the only functional difference between the two is in the relative degree of obstruction produced. The stenotic lesions along with the errors of rotation carry a lower mortality rate than the complete atresias, as reflected in Table IV.

TABLE II—*Intrinsic Defects*

	Cases	Deaths	Mortality
Duodenal	8	5	62%
Duodenal and extrinsic	4	3	75%
Ileal	14	11	78%
Colon	2	2	100%
Totals	24	18	75%

It has been generally assumed in the literature that the duodenal atresias offer a better prognosis than do ileal atresias. When the cases in our series which demonstrated both extrinsic and intrinsic lesions of the duodenum are grouped with the duodenal lesions, the apparent difference between the two groups disappears, and they join the overall group of complete obstructions which produce a mortality of 75 per cent.

When our cases are grouped by years (Table III), it seems justifiable to conclude that the mortality has improved to some extent as a result of better and earlier diagnosis, more blood, and the use of antibiotics. In any con-

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clusions drawn from such figures, however, it must be considered that the relative incidence of cases of complete obstruction in any one group will considerably affect the mortality rate

TABLE III—*Comparative Mortality*

	Cases	Mortality
1924-1938	11	81%
1939-1948	33	51%*
1944-1948 (U H)	20	35%†

* During this interval supportive therapy was significantly improved

† In this group earlier diagnosis was a probable factor. The fact that this group included 33 per cent intrinsic lesions as compared with 64 per cent intrinsic lesions for the entire series may have influenced the mortality also

Table V shows some of the possible causes of mortality which the surgeon can improve. Even if it were theoretically possible to eliminate all these, however, the surgeon would still be handicapped by the incidence of prematurity and associated cardiac defects.

TABLE IV—*Factors in Mortality*

Of infants known to be premature mortality was	60%
Of infants with associated anomalies chiefly cardiac mortality was	92%
Those with complete obstruction, mortality	75%
Those with incomplete obstruction, mortality	50%

There was no direct correlation between the age of the infant at the time of operation except in the case of intrinsic lesions where delay in operation seemed to influence the mortality.

SUMMARY

The chance of survival of the newborn infant with intestinal obstruction has increased during the past quarter century due to improved diagnostic, supportive and operative technic, but not to the extent achieved in adults.

TABLE V—*Factors in Mortality of Particular Concern to the Surgeon*

Tabulation of Possible Surgical Errors in Authors' Series		
Incomplete operation		11
Inadequate blood		4
Technical errors		
Poor choice of anastomosis	1	
Stomach not decompressed	2	
No complementary ileostomy	6	
Ileostomy only	3	12
Total		27
Less causes duplicated		4
Net total		23
Total deaths in series		25

We have presented a group of cases from three large urban hospitals, operated upon by a number of surgeons, and have reviewed some of the errors in management that may have contributed to the high mortality rate.

Diagnostic methods have been summarized. The history and physical findings are usually characteristic and are verified by roentgenograms.

The administration of blood and electrolyte solution before, during, and after the operation is of prime importance.

Factors contributing to high mortality rate are the high incidence of prematurity and cardiac anomalies, delay in diagnosis and hence operation, inadequate supportive therapy, and inadequate or unphysiologic operative management.

The most significant single factor seems to be the presence or absence of complete obstruction.

Surgical errors rank high as probable causes of failure.

Penicillin given before, during, and after operation reduces the incidence of peritonitis.

Anesthesia, surgical approaches, and specific operative procedures are probably less important in determining results than are a thorough understanding of the anatomical and physiological problems peculiar to the lesions. Completeness in exploration, and the use of primary, definitive surgery together seem to offer the best chance for survival of the infant. Partial procedures are to be avoided at all cost. The use of postoperative decompression is of major importance.

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DISCUSSION—DR THOMAS H LANMAN, Boston I think this presentation by Dr Glover shows what can be done with careful technic and careful attention to the many minute details so necessary to success in dealing with these young patients His results are remarkably good and though ours at the Children's are perhaps a little better, I think it will be only a short while before ours may be surpassed by those of Dr Glover

The important thing, when dealing with these malrotations, is a clear understanding of the embryology Not until this fundamental knowledge was appreciated did we get any lowering of the mortality in midgut volvulus, associated with malrotation In the other conditions, Dr Glover's figures correspond with ours, in that the higher the atresia or stenosis, the better are the results We have had a 61 per cent recovery in the cases of obstruction in the duodenum Decompression proximal to the lesion, I think, is of great importance, but in our experience the nasal catheter to the stomach seems to be better tolerated than Dr Glover has mentioned We do not sew a catheter in the bowel or stomach routinely as he has described, and believe that in most cases it is not necessary or desirable

In the cases of malrotation, as you have seen from the motion picture, it is vital to obtain a very wide exposure and so be able to see very clearly just what the condition may be It is futile to attempt to see or to treat what is wrong, through an inadequate incision

An understanding of the embryology has resulted in very much better treatment, but we must go further in our studies of the underlying cause of these conditions In looking over our cases to bring them up to date last year, we came across a rather disturbing fact It suggests the importance of the basic underlying cause of all these malformations As Dr Glover pointed out, these anomalies often are multiple In considering associated anomalies, the disturbing fact is this

In our last 17 recoveries in the surgical treatment of duodenal atresia, four patients

now are proved Mongols and two others are mentally deficient. These cases are now three to five years after operation. Obviously one cannot, with any security, make a diagnosis of Mongolian idiocy on the first day of life, though in two of these cases, we did record this possibility.

We must go on improving our surgical technic, our knowledge of fluid balance, and all those details which are of such great importance to surgical success. We must not discourage attempts to cure these malformations, but I do think that the coming generation should be stimulated to find out *why* they occur, and to me this is now the greater challenge.

We have a high per cent of mentally deficient patients in this recent series of successfully operated cases. Perhaps one could argue that these children were born 20 years too late, because 20 years ago they would, presumably, all have died. I do not agree with such a premise, but rather I believe we should go further in the study of these conditions than in the mere improvement of surgical technic.

I would prefer to accept this challenge of the need for further study than to take a rather simpler explanation that was offered to me last evening by a colleague, who remarked that these figures on mental deficiency merely confirmed his impression that Boston was no longer an intellectual center.

DR EDWIN M. MILLER, Chicago. Mr. Chairman and Gentlemen, I hesitate to discuss this interesting paper of Dr. Glover for fear of not being able to add anything of real importance. Great strides, indeed, have been made in this field since the first successful operation for atresia of the small bowel by Fockens of Rotterdam in 1911, and several members of the American Surgical Association have made worthwhile contributions, particularly Dr. Ladd, Dr. Gross, and Dr. Lanman of Boston and Dr. Donovan of New York, Dr. Wangenstein of Minneapolis, and Dr. Willis Potts of Chicago.

As I see it, the all-important thing is early diagnosis, and in order to obtain an early diagnosis the chief problem is to bring the matter effectively to the attention of those who first see these little infants with congenital obstruction, namely, the obstetrician, the pediatrician, and the men in general practice.

I would like to point out one or two things which are important.

1. The use of barium by mouth is not advisable in making a diagnosis and is not necessary, as a plain x-ray film of an atresia of the duodenum will clearly show the stomach and duodenum distended with air, and if the obstruction is in the small bowel, the dilated loops will be easily seen. The value of barium, if used at all, is when employed by enema, as then it will help to rule out an obstruction in the rectum or at the anus, and when it flows freely into the large bowel will reveal the pressure or absence of an incomplete rotation of the colon, thus giving information very important to the surgeon.

2. It is imperative before operation to deflate the obstructed bowel with a Levine tube or a small-sized (No. 12) Miller Abbott tube if possible, in order that the abdomen can be widely opened and the obstruction adequately dealt with so that the use of an ileostomy may be avoided.

These points are here emphasized by four lantern slides which show (1) the ease of diagnosis of an atresia of the ileum by the plain x-ray film, (2) the successful anastomosis after adequate deflation of the bowel, (3) the good progress of the infant about six weeks later, and (4) the G. I. follow-through with barium by mouth three months after surgery.

The moving pictures shown by Dr. Glover in dealing with a high obstruction due to volvulus and malrotation have been very instructive.

DR WILLIS J. POTTS, Chicago. The history of one of three similar patients seen recently is interesting in connection with this subject of intestinal atresia so well presented by Drs. Glover and Barry.

This three-day-old child had all the signs and symptoms of congenital atresia of the bowel. The x-ray picture (slide) shows typical dilated intestinal loops containing fluid levels. The infant had had no bowel movement. During the operation under ether anesthesia the infant passed a huge meconium stool. No obstruction was found and the abdomen was closed. Attention was promptly called to an article which appeared in the American Journal of Diseases of Children in January, 1948, by Zuelzer and Wilson of Detroit, "Functional Intestinal Obstruction on a Congenital Neurogenic Basis in Infancy." Their description of cases showing all the signs of congenital atresia of the bowel but actually having no mechanical obstruction made the diagnosis for us. Typically the infant again developed signs and symptoms of complete intestinal obstruction requiring a transverse colostomy.

Since the area of agenesis of the myenteric plexus is usually confined to the descending colon it has been advised that the descending portion of the colon be resected later and that the transverse colon be anastomosed to a suitable stump of the rectum.

DR DONALD M. GLOVER, Cleveland. We are much indebted to Dr. Lanman, Dr. Miller and Dr. Potts for their discussion.

In regard to Dr. Lanman's comment that at the Children's Hospital they have had little difficulty with the presence of a tube in the baby's pharynx, I must admit that we have also had some patients who seemed to tolerate it fairly well. Some of them, however, develop edema of the pharynx from the presence of the tube, and in some instances there was tracheal aspiration of regurgitated gastric contents which we believed was at least partly due to the presence of the tube. We do not at present have bilumen tubes small enough to be satisfactory for use in small infants, and it seems safer to have feeding and aspiration tubes inserted through the gastric wall than to depend upon a tube introduced through the pharynx which can serve only as a feeding tube or an aspiration tube, but not both.

Dr. Lanman has called attention to the associated defects. We hope that the present efforts of the obstetricians and internists to prevent prematurity and maternal infections during pregnancy may reduce the incidence of these defects.

Referring to Dr. Miller's comment about ileostomy, there have been at least two cases reported where survival has followed the primary use of ileostomy alone. Dr. Miller also raised the question about the possibility of future obstruction in cases of malrotation and volvulus in which the colon and duodenum have been freed from their lateral peritoneal attachments. Among the last ten cases operated upon in this manner, we have had one case of recurrent obstruction which was not, however, due to denudation of peritoneum. A number of cases will be found in the literature which demonstrate the possibility of a recurrent obstruction where the colon and duodenum have not been completely mobilized, as advised by Ladd. From the patients we have had an opportunity to follow, we have encountered no difficulty from deperitonealization. We have been impressed with the fact that the peritoneum of the newborn infant covers defects rapidly.

The question as to whether or not the colon should remain on the left side, in the fetal position, has been argued. Dr. Ladd feels that it should and most of us, I believe, feel that it is safer in that position. We have on occasion, however, deliberately placed the colon on the right side of the abdomen without fixing it in any way and subsequent roentgenograms, taken years later, have shown that the cecum remained in its normal position on the right side although the duodenojejunal junction retains its vertical position.

The interesting case presented by Dr. Potts brings up several important points which, due to time limitations, we shall not attempt to discuss.

GASTRO-INTESTINAL GAS

OBSERVATIONS ON BELCHING DURING ANESTHESIA, OPERATIONS AND
PYELOGRAPHY, AND RAPID PASSAGE OF GAS*

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STUDIES ON THE ORIGIN of gastro-intestinal gas support the theory that swallowed air is its chief source. The literature on the subject is voluminous and only a few pertinent articles will be referred to.

Kantor¹ in 1918 presented the older historical background on the subject and Alvarez's² comments are thorough and interesting. McIver, Benedict and Cline³ in 1926 showed that cats with peritonitis had considerable gaseous distention of the stomach and intestine, but if the pylorus was ligated at the time of the peritoneal contamination, then the stomach was dilated without distention of the intestines. The importance of swallowed air was obvious, and, using gastric suction in patients, these authors were able to reduce materially the incidence of postoperative distention. Wangenstein⁴ in 1932 instituted the very important use of continuous gastro-duodenal suction-siphonage in decompressing certain types of acute mechanical intestinal obstruction, and with Paine and Carlson⁵ in 1933 showed that the same procedure would often remove from 2000 to 3500 cc of gas daily from postoperative surgical patients, and thus markedly reduce the incidence of postoperative distention. Wangenstein and Rea⁶ in 1930 presented their classical experiment further indicting external air as the main source of gastro-intestinal distention by showing that the gas content of obstructed ileal loops in dogs was greatly reduced if at the time of producing the obstruction the cervical esophagus was also divided and the distal end closed. In earlier experiments it had been learned that if the distal end was left open the animal swallowed as much air as a dog with the esophagus intact. Singleton, Rogers and Houston⁷ in 1942 stated that postoperative distention in patients undergoing abdominal operations did not occur as long as continuous suction was applied through an inlying gastric tube. They emphasized the prevention of gaseous distention by the preoperative institution of the procedure rather than its use to relieve distention later. The present widespread use of this valuable advance in abdominal surgery is due to the work of these various investigators.

The authors' interest in this subject centers mainly on how atmospheric air enters the esophagus and stomach. Actual swallowing of air does play a part in many cases, but there must also be other mechanisms involved, particularly to account for the occasional large and rapid accumulations of ga

* Read before the American Surgical Association, St Louis, Mo., April 21, 1949

Morris, Ivy and Maddock⁸ noted the paucity of observations on actual swallowing of air by distended patients and reviewed pertinent comments on acute gastric dilatation, air-sucking and esophageal speech, conditions under which air is known to enter the esophagus and stomach without swallowing. In order to study possible mechanisms involved they attempted by a large number of animal experiments to produce acute gastric distention, but were unable to do so with any degree of constancy. Using human subjects, however, they were able to show that

- 1 Attempting actively to breathe against a closed glottis can produce negative pressures in the esophagus and stomach up to 30 cm of water

- 2 The superior esophageal constrictor is a very important sphincter normally closed, but opening on deglutition to allow food and drink to pass into the esophagus. This sphincter can be relaxed consciously by some individuals and unconsciously by others. The muscular tube of the esophagus is interesting in that at least the upper part is striated.² The superior esophageal sphincter was first described by Killian⁹ in 1908 and is found at the pharyngeo-esophageal junction where a fold of mucosa and the transverse fibers of the inferior pharyngeal constrictor muscle form the sphincter.

The combination of the negative pressures stated in (1) above and intubations or relaxations of the superior esophageal sphincter permitted the following observations. In reading them over it is evident that the processes described are all of the same nature, with only minor variations, depending upon ways of opening the sphincter and how the negative intra-esophageal pressure was produced.

- 3 With the superior esophageal sphincter intubated with a Levine tube to the stomach, the negative pressure of each attempt to breathe against a closed glottis easily drew from 50 to 160 cc of air from a spirometer into the stomach. With a few such efforts gastric gas quickly amounted to 400 to 500 cc.

- 4 With the superior esophageal sphincter relaxed, as can be done by many individuals, the negative pressure of attempting to breathe against a closed glottis easily drew 1000 to 2000 cc of air into the esophagus in a period of three to five minutes. "Air-suckers" to us are individuals who know they can do this, and control the act. "Aerophagics" carry out the same procedure, but are the highly nervous or hysterical individuals who do not know or will not recognize what they are doing to ingest air. The relationship between nervousness and gastro-intestinal gas has been stressed by many authors and will be emphasized later in this paper.

- 5 With the superior esophageal sphincter partially relaxed, as in sleep, attempting to breathe against an obstructed airway—tongue dropped back and snoring—resulted in the aspiration of air into the stomach.

- 6 Along with learning how to relax the superior esophageal sphincter the laryngectomized patient can place a finger over the tracheotomy opening and on trying to breathe produces an increased negative intra-esophageal pressure which draws air into the esophagus, and stomach to some extent. With con-

trolled eructations of the air "esophageal speech" is possible. The intake procedure is fundamentally the same as air-sucking.

7 When the superior esophageal sphincter is intubated with a Levine tube to the lower esophagus the negative pressure of respirations can easily draw air in from a spirometer. For five subjects the following average amounts were so aspirated per minute: normal quiet respirations—39.5 cc, moderately deep respirations—43.7 cc, deep respirations—91.9 cc.

The esophageal speech patient with practice no longer needs to place his finger over the tracheotomy opening to take air into the esophagus but learns to "aspirate" or "inspire" the air with respiratory movements, as done by the above subjects.

From these observations the importance of the superior esophageal sphincter, and the effect of respiratory movements in the mechanism of air entry into the upper gastro-intestinal tract, are apparent. It is believed that

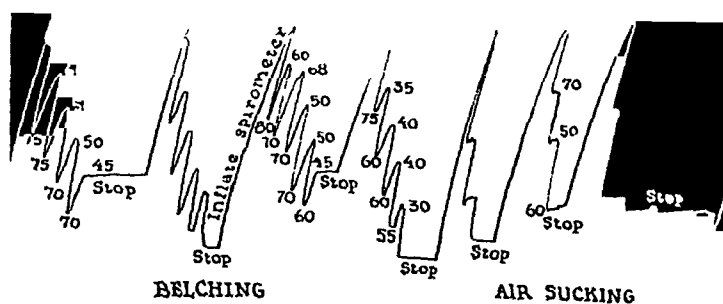


FIG 1—Air exchange with belching and air sucking. With belching some air is retained, the aspiration figures in cubic centimeters on the left side being greater than the eructation figures on the right side. When asked to suppress the eructations and perform air-sucking for three efforts a total of 180 cc were aspirated. A B was then unable to hold the air and felt some discomfort. A voluminous belch followed.

many conditions, intra-abdominal and elsewhere, may originate reflexes changing the tone of the sphincter and varying respiratory movements with resulting aspiration of air into the esophagus and stomach. The great diversity of diseases in which acute gastric dilatation has occurred⁸ support the opinion that a reflex phenomenon is involved. In many instances it may be discomfort, nervousness, and apprehension associated with the disease or injury and its treatment, that starts the unconscious aspiration of air.

To learn more about gas in the gastro-intestinal tract this paper presents studies on (1) belching, (2) swallowing movements, and the entrance of air into the stomach during anesthesia and operations, (3) the rate of passage of air through the gastro-intestinal tract and (4) meteorism during pyelography.

BELCHING

Alvarez² lists six different kinds of belches and points out that many of the individuals afflicted with more than the usual polite belch after a meal

are nervous, worried, irritable, distracted and hyperactive people. He has frequently seen the chronic belcher under the fluoroscope and notes that most of the air stays in the esophagus and does not descend into the stomach.

Frequent belching is a modification of air-sucking or aerophagy. The individual who can repeatedly belch on request knows how to relax the superior esophageal sphincter, does so, and then tries to breathe in with the glottis closed.¹⁰ The air thus entering the esophagus is immediately belched back. The subconscious or unintentional frequent belcher is invariably a nervous individual who does about the same thing, probably taking in the air by a less apparent respiratory effort.

It is known that frequent belching often produces a sense of fulness in the epigastrium and probably is the source of considerable amounts of air entering the stomach. Belching was therefore studied to obtain some quantitative data.

TABLE I—*Summary of Air Exchange with Belching*

Subject	No of Belches	Cc of Air					
		Aspirated		Eructated		Retained	
		Total	Av	Total	Av	Total	Av
1	9	815	91	760	84	145	16
2	8	235	29	200	25	35	4
3	8	710	89	405	51	305	38
4	13	580	45	470	36	110	8
5	18	740	41	335	19	405	23

(Frequent belching can result in the retention of considerable air. With a patient lying down this can easily pass into the intestines and produce distention.)

Method Normal young males who could belch at will were used in this experiment. They performed the act with the nose closed by a soft clamp and the mouth closed around a glass tube connected to a recording spirometer and kymograph.

Result It was easily demonstrated, as has been described before, that these voluntary belchers take in air by air-sucking and then immediately eruct the air. Two distinct sounds can be heard with this process,¹ the first with the air entering and the second as it is belched back. "Cribbing" in horses is the same process,^{10, 10a} and Wyllie similarly described the two sounds.

A typical kymograph tracing (Fig 1) shows that with belching the amount of air aspirated into the esophagus was greater than the amount of air eructated and some air probably passed into the stomach.

A summary for the five subjects of this experiment is shown in Table I. The totals and average amounts of air aspirated, eructated and retained are quite impressive and, with the subject lying down, this air could easily pass into the intestines and produce distention.

Belching often comes on as a manifestation of nervousness, and Fig 2 shows marked gastro-intestinal distention in a nervous and apprehensive surgical patient who was repeatedly belching. It is recalled that in previous

years it was not uncommon to ask a patient with distention if he were passing gas rectally and to have him answer, "No, but I am belching up gas." With the data of this study it is realized that the belching may have been the process responsible for the distention.

AIR INGESTION DURING ANESTHESIA AND OPERATIONS

In their study of postoperative distention McIver, Benedict and Chinc³ considered the rather frequent finding of gas in the stomach and stated that "It is well known that a great deal of air may be swallowed during the early stages of anesthetization." They observed 115, 67 and 54 swallowing move-



FIG 2—Marked gastro-intestinal distention in a surgical patient from repeated belching. There was considerable passage of flatus during the time of the distention. When J. S. stopped belching by request the distention rapidly subsided.

ments in three patients undergoing etherization, but no measure was made of the amount of gas taken into the stomach with these swallows. On the other hand Davis and Hansen¹¹ determined the amount of air taken into the stomach during operations and concluded that much of it entered during the induction of anesthesia, but no record was made of swallowing or other possible modes of gas entrance.

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It was our impression that frequent swallowing did not take place during the course of an anesthetic and operation, yet occasionally the stomach distended with air during that time. To learn more about swallowing and to repeat Davis and Hansen's work, a series of 23 patients was studied.

Method A Levine tube was inserted into the cardiac end of the stomach from 60 to 90 minutes prior to the induction of anesthesia. Continuous suc-

TABLE II—*Air Ingestion During Anesthesia and Operations*

Number Sex and Age				Operative Procedure	Induction Period			Operative Period		
					Time Min	Swal- lows	Gas Cc	Time Min	Swal- lows	Gas Cc
Group A Spinal and Pentothal Anesthesia										
1	F	57	Lysis abd adhes	20	0	0	74	1	100	
2	F	49	Abd perin res	20	0	0	178	0	75	
3	F	73	Abd perin res	20	0	0	136	0	120	
4	F	55	Abd perin res	10	0	0	210	0	100	
5	M	61	Amput thigh	15	0	0	55	0	30	
6	F	38	Cholecystect liver biopsy	10	0	0	78	0	50	
7	M	74	Abd perin res	22	0	0	206	0	780	
Group B Inhalation Anesthesia NO ₂ or C ₂ H ₄ or C ₃ H ₈ + O ₂ + ether										
8	M	63	Cholecystectomy	8	0	0	116	0	130	
9	F	62	Cholecystectomy and appendectomy	8	2	0	90	0	70	
10	M	39	Cholecystectomy and resection duod divert	5	3	30	135	0	0	
11	F	52	Cholecystectomy choledochostomy	5	3	50	86	0	25	
12	F	71	Transverse colos	4	0	0	55	0	0	
13	F	54	Choledochostomy	10	2	50	88	0	50	
Group C Cyclopropane and Curare										
14	F	57	Cholecystectomy choledochostomy	6	0	0	120	0	130	
15	M	56	Cholecystectomy	4	3	0	116	0	0	
16	M	62	Cholecystectomy	5	0	0	86	0	0	
17	M	49	Splenectomy	7	0	0	98	0	0	
18	F	47	Cholecystectomy appendectomy	6	0	0	98	0	25	
Group D Cyclopropane and Curare										
19	M	39	Gastroenterostomy Vagotomy	9	3	75	170	0	385	
20	F	70	Cholecystectomy	4	2	50	60	0	825	
21	F	57	Cholecystectomy excl lipoma stomach	4	1	10	113	0	1600	
22	F	53	Ventral hernia	6	0	20	177	0	1700	
23	M	30	Partial gastric resection	6	5	50	204	0	250	
Average					1	0	14	5		
For inhalation anesthesia					1	5				

Important Findings 1 Swallowing movements were infrequent 2 Air intake high with obstructed respirations—case 7 3 Air intake high with curare plus positive pressure anesthesia

tion was applied immediately to empty the stomach and was continued throughout the remainder of the preoperative and operative period. By measuring the amount of water displaced in the upper bottle of the Wangensteen suction apparatus, the amount of gas returned from the stomach was determined. The anesthetist* counted the swallowing movements during

* This work was done with the assistance of Dr Mary Karp, Chairman of the Dept of Anesthesia Wesley Memorial Hospital, and will be reported later in detail with her

the induction of anesthesia by placing a finger over the patient's larynx. One of us (J B) recorded the amounts of gas returned, and the coincident actions of the patient, the surgeon and the anesthetist for the remainder of the procedure.

Results Of the 23 patients studied, all operations except one, No 5, were laparotomies. The usual preoperative medication consisted of morphine sulfate 10 mgm and atrophine sulfate 0.4 mgm.

From the summarized data shown in Table II it is evident that during the swift induction of a modern inhalation anesthetic there are very few swallowing movements, our average of 1.5 per patient being far less than the 79 average observed by McIver, Benedict and Cline³ during the longer induction of an ether anesthetic. We believe these swallowing movements are largely manifestations of nervousness and they did not result in appreciable amounts of gas entering the stomach.

During the operations only small amounts of gas entered the stomach of the majority of patients. Excluding the exceptions, patient No 7 and all those of Group D which will be discussed further, our figures of 0 to 130 cc, average 53 cc, are less than, but not significantly different from, Davis and Hansen's¹¹ average of 143 cc.

Patient No 7 of Group A had a 780 cc intake of air during the operation, which we believe was due to his attempts to breathe against a closed glottis. The observer noted that the jaw dropped occasionally during the operation and there was a snoring and partially obstructed respiration. Air could thus not easily pass into the trachea, and the negative intra-esophageal pressure aspirated air downward to the stomach. We have seen distention develop in other patients with an obstructed airway. This factor, along with the more important one of decreased oxygenation and cyanosis, give great reason why the respiratory passages must be kept open.

It was noted by the observer that the ordinary manipulations of the viscera attendant upon an abdominal operation did not result in gas entering the stomach.

The patients of Group D were of special interest. Their anesthetic was cyclopropane and curare, the same as Group C, but 250 to 1700 cc of gas were aspirated from their stomachs. The D group had some intercostal paralysis following the injection of curare and slight positive pressure was used to augment respirations. It was thought that the curare considerably relaxed the superior esophageal sphincter and this, plus the pressure anesthesia, forced some gas into the stomach.

Anesthetists have long known that gastric dilatation is a common complication of positive pressure anesthesia and recently¹² a warning was given to be ready to aspirate air from the stomach when curare is used.

The results of this experiment fit well with clinical experience. At most laparotomies there is no troublesome distention of the stomach, but occasionally it is observed by all surgeons, and it occurs without swallowing. Luckett,¹³ in reporting a case in which acute distention occurred during surgical treat-

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tated, "I could distinctly feel and hear large gulps of air entering my stomach, and hear a noise in the throat, yet the patient was not swallowing, the thyroid cartilage was apparently still and there was no visible distention in the throat."

A remarkable case report was recently received¹⁴ in which the patient had aspirated air into the esophagus with resulting distention and spontaneous rupture of the stomach. Roentgenograms of the consequent enormous pneumoperitoneum, and a brief description of the case, are given in Fig. 3. There can be no doubt that relaxation of the superior esophageal sphincter and voluntary aspiration of air blew this patient up.



FIG. 3—Enormous pneumoperitoneum following spontaneous rupture of a stomach distended by inspired air during a minor operation under sodium pentothal anesthesia. G. H., a woman, age 47 years, was admitted to the hospital on June 16, 1947, for removal of a root fragment of the right first lower premolar tooth. A chronic draining sinus at that point necessitated the surgery. History and physical examination and laboratory data were otherwise normal. B.P. 134/78. Pre-operative medication was morphine sulfate gr 1/6 and atropine sulfate gr 1/150. The patient arrived in the operating room in good condition. B.P. 124/80. An intravenous sodium pentothal anesthesia using a 1 per cent solution was started at 8:10 A.M. and a total of 0.75 Gm. were given. Anesthesia to first plane appeared within 45 seconds. At 8:13 a Guedel pharyngeal airway was inserted and a sibilant, hissing sound audible to all those in the operating room was emitted by the patient. The sound resembled the hiss of an angered goose rather than the high pitched, strained crowing of laryngo-spasm. It persisted continuously, with only minor variations in intensity and was completely inspiratory. The anesthetist was quite certain that the airway could not have slipped into the esophagus. The anesthesia was otherwise uneventful, B.P. and pulse were normal. At 8:15 oxygen at 5 liters per minute was started through a small nasal catheter. "Moderate" abdominal distention was noted while draping the patient. At 8:15 the operation was started and finished at 8:27. "Enormous" abdominal distention was noted when removing the patient. The abdomen was tympanic and no intestinal sounds could be heard.

On return to the patient's room a Wangensteen tube was inserted, but no gas or fluid was obtained. B.P. was now 90/60. At 10:00 A.M. a second passage of the Wangensteen tube brought up a small amount of blood. Scout roentgenograms of the abdomen revealed a massive pneumoperitoneum. The diagnosis of a perforation of the stomach was made and the patient was returned to surgery for a laparotomy. When the abdomen was opened, air escaped under pressure with the sound of a tire being rapidly deflated. The peritoneal cavity was free of fluid, blood or food particles. The lower half of the stomach and duodenum were normal to inspection. The upper portion of the stomach was exposed and a 4.5 cm. longitudinal rent was found about 1 cm. anterior to the lesser curvature, the proximal end of the tear being 2.5 cm. below the cardio-esophageal junction. This was an edged tear was through normal stomach tissue. It was closed and the patient made an uneventful convalescence.

THE RAPID PASSAGE OF AIR THROUGH THE GASTRO-INTESTINAL TRACT

Gastro-intestinal gas that appeared quickly was disturbing to us at one time because the source as "swallowed air" was not readily apparent. But with a better understanding of air sucking, aerophagy, belching, the action of the superior esophageal sphincter, and negative esophageal pressures from inspiratory efforts, the possible mechanisms of the rapid flow of air down the esophagus became evident. Fortunately, the rapid accumulations of gastric gas, rather than the slow increments, offered the best chance of observing how and under what conditions it entered the esophagus. In this regard many comments have been made on the marked increase in intestinal gas frequently seen in the short time from the first to the last roentgenogram of patients undergoing pyelography. Many observers—radiologists, urologists, etc.—accept the general impression that "swallowed air" is the source of this gas the same as in other flatuosities. Oppenheimer¹⁵ and Begg,¹⁶ however, offer different theories.

Oppenheimer¹⁵ in 1940 noted that excessively large amounts of gastro-intestinal gas appeared during retrograde pyelography when this procedure produced pain, and this led him to study the relationship between pain and gaseous distention. He found that in 82 instances of severe pain, such as with fractures of the extremities and spine, gonococcal arthritis, sciatica, lumbago, toothache, trigeminal neuralgia, herpes zoster and dislocations no gaseous distention was observed. On the contrary, in numerous cases of renal colic, biliary colic, duodenal ulcer, acute appendicitis and salpingitis the type of gaseous distention was identical with that found during retrograde pyelography. In 14 of his patients with urinary disease intravenous pyelography was done with complete absence of pain, yet gaseous distention developed. Accordingly, Oppenheimer believed that pain in itself was not responsible for the appearance of gas in the bowel, but that some abdominal diseases may cause both pain and gaseous distention.

Oppenheimer observed roentgenographically in man that ureteral catheterization and distention of the renal pelvis with fluid or oxygen was followed by rapid overfilling of the stomach, small intestines and colon with gas, and stated that the large amounts seen within a few minutes could not possibly be due to abnormal fermentation or diffusion from the blood stream. To account for the source he offered the thesis that the small amount of gas always present in the intestines quickly expanded to fill the intestines when they became atonic due to inhibitory reflexes which arise from renal or biliary colic, pyelography, etc.

This thesis is untenable because a given amount of gas cannot expand into a larger space without a reduction in pressure and the soft intestinal tube and flexible abdominal wall will not be supported in reduced pressure. Except for moments of active peristalsis intestinal gas pressure is close to atmospheric pressure.

Begg¹⁶ in 1948, in writing on a rational theory of intestinal distention and its urological application, contended that gas pains and distention may be

completely obviated provided nothing whatever is given by mouth or rectum during the inevitable postoperative non-peristaltic period. He did not believe that distention was due to air swallowed during and after the operation for the following reasons: (1) The theory is inapplicable to distention accompanying spinal lesions, lightning stroke, renal colic, anuria, etc., unless one is to suppose that the victims become suddenly addicts to aerophagy. (2) It is incompatible with the observed fact that postoperative patients do not distend if given no fluid, no matter what air they may have swallowed. He further stated that if it were contended that the air was swallowed with the fluid, it would be hard to imagine that a single drink would initiate progressive and increasing distention as he has observed.

Thus, finding the swallowed air theory to be unsatisfactory, and the role of food fermentation disproved, Begg considered the only remaining possibility to be gas derived from the blood, and nitrogen the important gas, it being available to the bowel by "intestinal respiration" and absorbed if it is in excess. The passage of nitrogen to the bowel and back to the blood depends on the physical laws of diffusion of gas, and Begg considered that any factor which, when the dynamic function is in abeyance, reduces the tonus, increases the potential capacity of the bowel lumen and permits the inflow of gas. He stated further that fluids and food reaching the stomach during the postoperative refractory period cause this organ to contract on its contents, leading to a reflex reduction in tone of the intestines which enables the blood gases to flow in to fill the increased space in the lumen. He cited the marked increase in intestinal gas when an ureteral catheter is passed, and the quick influx of gas into the bowel following the injection of Uroselectan, as further evidence of the theory of rapid diffusion of nitrogen into the bowel, given the requisite conditions.

The authors believe that giving nothing by mouth to postoperative patients reduces the possibility of gaseous distention, but certainly does not eliminate it entirely, and relative to Begg's opinion that swallowed air cannot be the main source of gastro-intestinal gas unless "the victims become suddenly addicts to aerophagy" the evidence of this study shows that this is exactly what may take place, if one uses the term aerophagy in a broad sense covering the esophageal ingestion of air without swallowing.

The time element for the accumulation of large amounts of air in the stomach is known to be rapid in acute gastric dilatation,⁸ air-sucking and aerophagy. The time element for the almost immediate passage of gastric gas into the small intestine and its arrival at the cecum and anus within a few minutes is not well known. Usually gas is not thought of as passing along any faster than food. Actually it does, and this point was first studied by Magnusson.¹⁷

In 1931 Magnusson was interested in meteorism in pyelography. He dismissed gas formation from intestinal decomposition and diffusion from the blood as possible sources and believed that the main bulk of the gas consisted of air that had passed down the esophagus, probably by some

process of aerophagy or air-swallowing Magnusson's important point was that to account for the rapid colonic meteorism in pyelography the "swallowed air" must pass out of the stomach and through the small intestine in a very short space of time To confirm this impression he filled the colon of normal adult subjects with an opaque enema so that air coming into the cecum could be easily seen He then turned the subjects on their left side to place the pylorus upward and injected air into their stomachs The progress of the air was determined by frequent roentgenograms and the results are shown and compared with the passage of food in Fig 4

It was considered that a further investigation of this rapid air passage should be carried out

Method For these experiments young, male, medical students were used No purgatives or enemas were given and a normal breakfast was eaten about three hours before the experiment An initial scout film of the abdomen showed the existing amount of gastro-intestinal-gas, and usually the stomach was found empty A 16 F Levine tube was then introduced

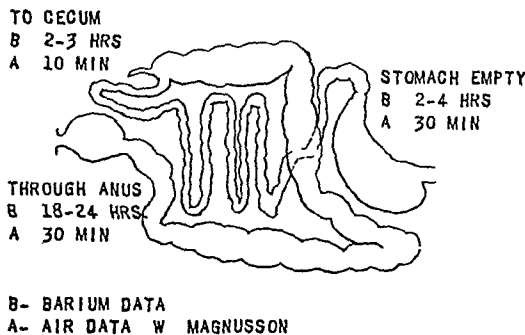


FIG 4—Diagram showing the rapid passage of air compared to barium through the adult gastro-intestinal tract (W Magnusson¹⁷)

through the nostril into the middle esophagus a distance of about 30 cm, and was connected to a graduated spirometer by a tube having a one-way valve allowing gas to pass only in the direction of the esophagus The subjects then lay on the radiographic table on their back or side just as they wished In most subjects a 30 F mushroom catheter was inserted into the rectum and flatus collected by means of a water displacement apparatus The spirometer was then filled with air, 100

per cent oxygen for one experiment and on moderately deep respirations the negative pressure produced in the esophagus drew air from the spirometer into the esophagus, from which it passed into the stomach

Besides the initial roentgenograms,* others were taken when 500 cc and 1000 cc of air had been aspirated and at later intervals to show the extent of the flatulence Careful records were made of the symptoms of the subjects cramping abdominal pains if any, the degree of abdominal distention as measured at the umbilicus, the time of first passage of flatus, and the total amount passed

Results The majority of subjects were allowed to aspirate 1000 cc of air which they did in about 30 minutes W H took in 1650 and 2000 cc in approximately the same time

It is suspected that more air may have entered the stomach of some sub-

* This part of the study was done with the assistance of Dr Earl Barth, Assoc Prof of Radiology, Northwestern University, and will be reported later in detail with him

GASTRO-INTESTINAL GAS

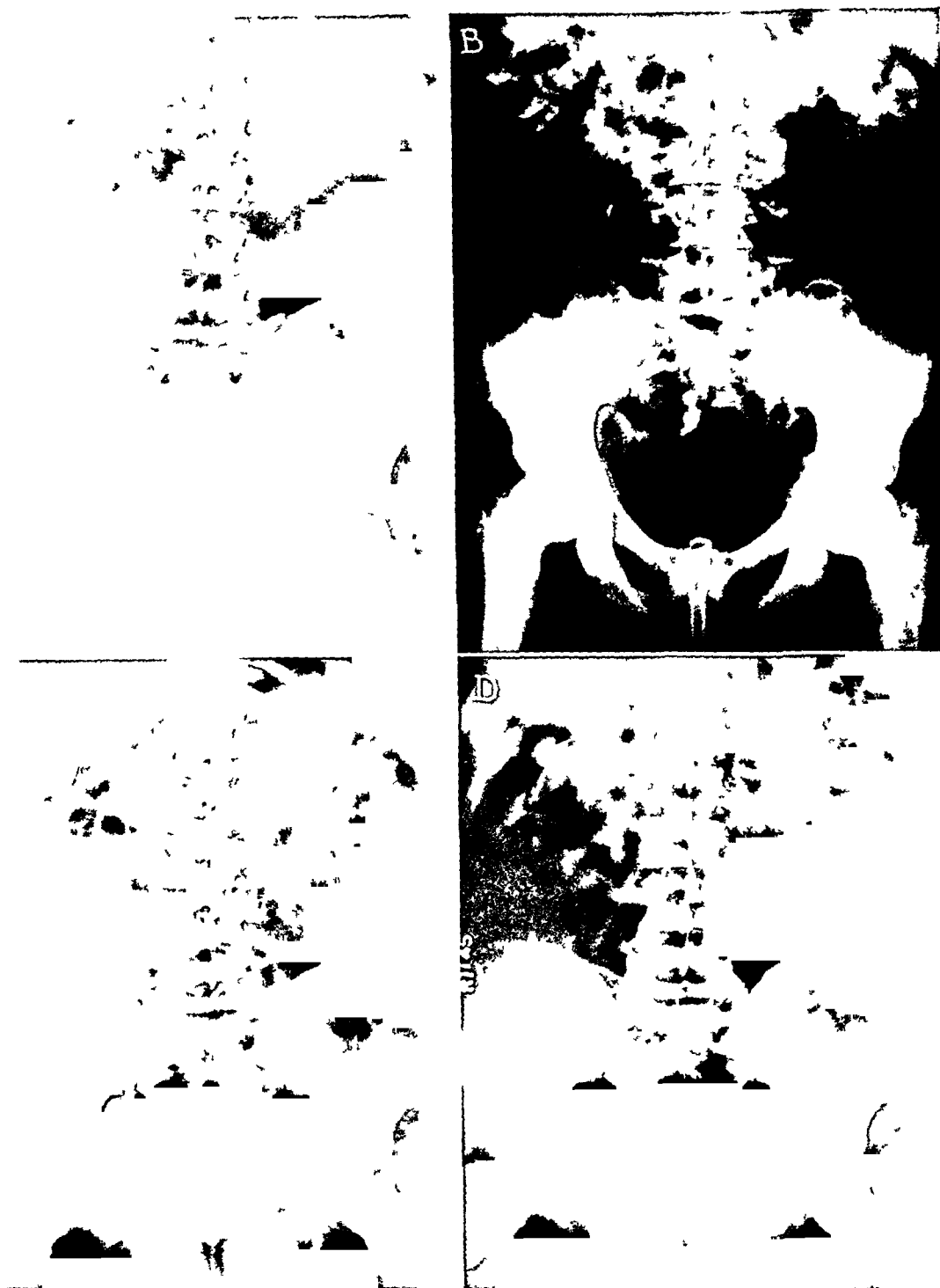


FIG 5—Roentgenograms showing rapid passage of 1000 cc of oxygen (L S²) (A) Before the passage of the Levine tube. No gas in the stomach or small intestine and only a small amount in the ascending and descending colon. Oxygen aspiration, which seemed to be no different than air aspiration, was then started. At 18 min increased gas was seen in the cecum by a following roentgenogram (B) At 28 min. Shows the distribution and distention produced by 1000 cc of gas. Esophageal tube had just been removed. Abdominal girth at umbilicus increased only 2 cm. At 36 min the first flatus was passed (C) At 53 min. Considerable gaseous distention although 500 cc of flatus had been passed (D) At 110 min. Less general distention but still some gas in the distal three-fourths of the colon. Flatus passed 800 cc.

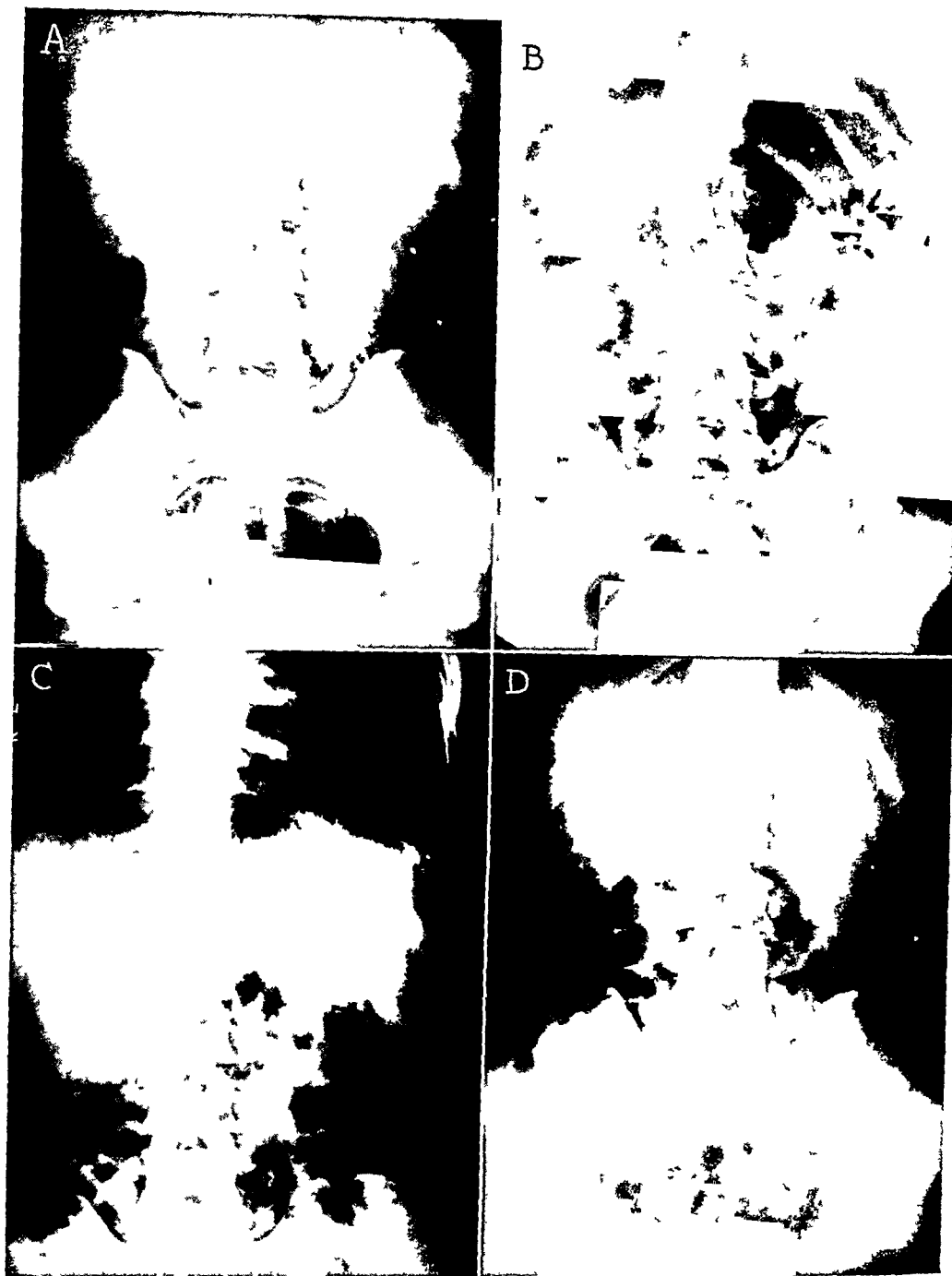


FIG. 6—Roentgenograms showing rapid passage of 2000 cc of air (W H)
 (A) Initial film showing only a small amount of gas in the cecum, descending colon and rectum (B) At 17 min, 1000 cc of air had been aspirated. The stomach and intestines are considerably dilated. The first flatus had just been passed. A previous film at 8 min showed the air had reached the cecum (C) At 37 min, 2000 cc of air in and flatus was being freely passed (D) At 110 min there is relatively little of the gas left, flatus having been voluminously passed for 93 minutes

jects around the Levine tube, so that the amounts discussed are probably not entirely correct in all instances. This will be pointed out later by specific examples.

The roentgenograms for a typical experiment are shown in Fig 5. This happens to be the subject in which oxygen was aspirated, but the results were the same for air. Roentgenogram B taken at 28 min., shows the wide general distribution and the distention produced by 1000 cc. of gas. Gas reached the cecum in 18 min., flatus was first passed at 36 min. and 800 cc. were collected in 74 min. Once started, the passage of flatus in this subject, as in others, was quite regular in time and amount, as would be expected by rhythmical peristaltic action. This is shown as follows:

Time of Passage Minutes	Amount of Flatus cc
36	100
40	100
44	100
47	100
51	100
56	100
62	100
70	50
80	0
90	25
110	25
74	800

Fig 6 shows the distention and rapid passage of 2000 cc. of aspirated air. Roentgenogram B is a good example of the distribution and distention produced by 1000 cc. Before 2000 cc. were ingested flatus was passing freely.

Fig 7 shows the result of administering prostigmine methyl sulfate. The time for the gas to reach the cecum was no different than without prostigmine, and other subjects passed flatus just as rapidly. Actually prostigmine did not clear the bowel of gas. It is true that more flatus was passed than the known amount of air aspirated, but at 125 min. there is considerable gas in the stomach and colon and some in the small intestine. It is believed that the subject continued to aspirate air long after the Levine tube had been removed. The same result was obtained with this subject in a later similar experiment. He was a stoical individual and little disturbed by what went on around him. The prostigmine may have disturbed the intestines and produced a reflex resulting in the esophageal aspiration of air. It has been noted by others² that an enema may be followed by the rapid accumulation of gas in the small intestine and colon. The enema may quite possibly have disturbed the intestines and/or the patient in general with a resulting reflex aspiration of air. The nervous factor is commonly seen in gaseous distention.

The summary of the data, Table III, shows an average of 1133 cc. of air aspirated from the spirometer by the negative intra-esophageal pressures of moderately deep breathing in 30.4 minutes. At 20 respirations per minute

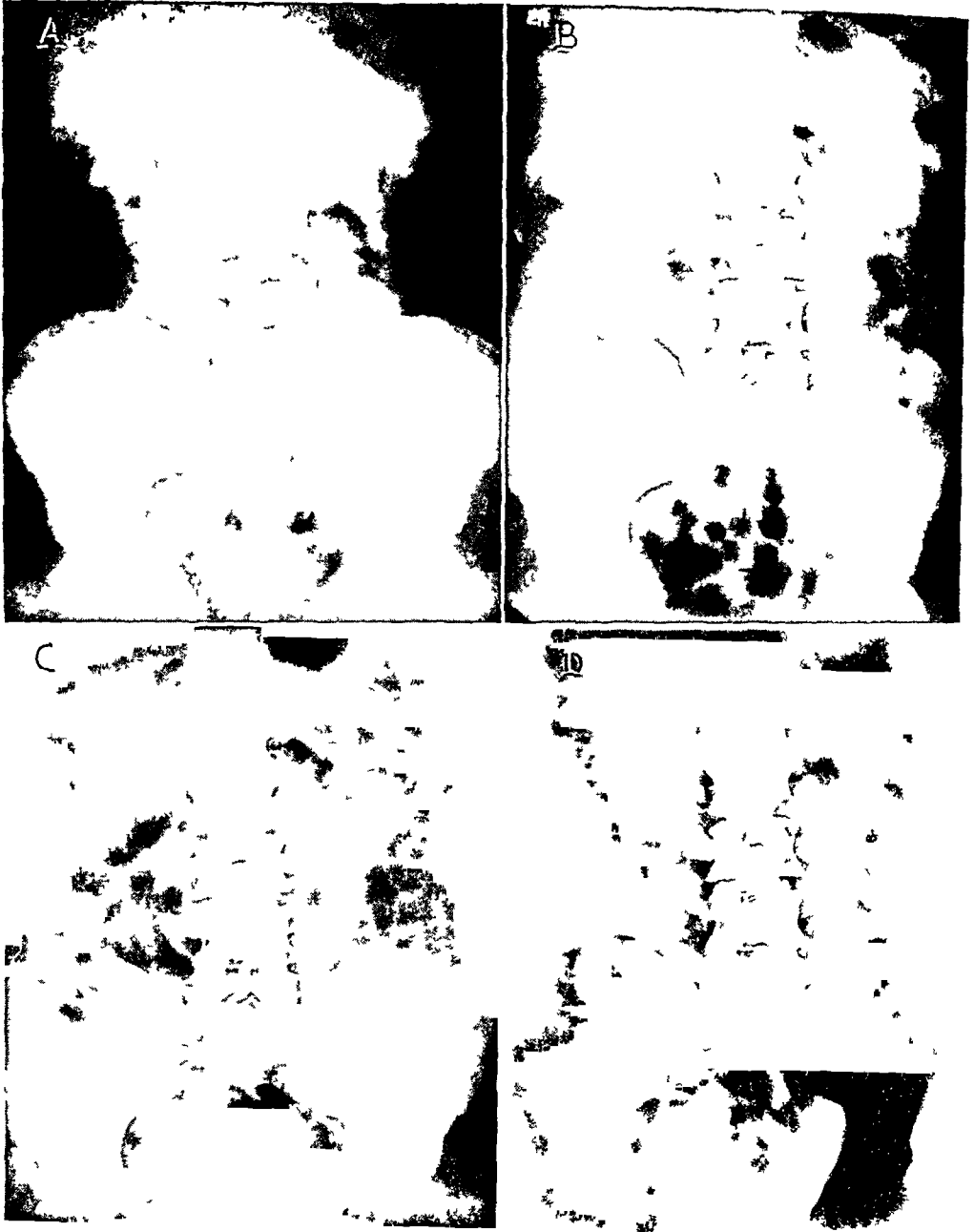


FIG 7—Roentgenograms showing effect of prostigmine on the passage of 1000 cc of air (V T¹). (A) Initial film, 6 min after the subcutaneous injection of 0.25 mg of prostigmine methyl sulfate. Small amount of gas seen scattered throughout the stomach and bowel. (B) At 25 min, 400 cc of air aspirated and first flatus just passed. Intestinal distention appears too extensive for that amount. (C) At 74 min, 1000 cc of air in and 850 cc of flatus passed. There is some gas in the stomach and considerable in the intestines. A second dose of 0.25 mg of prostigmine was given when 1000 cc of flatus had been passed. (D) At 125 min, 1150 cc of flatus collected, which is 150 cc more than the amount of air aspirated from the spirometer. There is still considerable gas in the stomach and colon, and a small amount in the intestines. More air must have been aspirated than came down the Levine tube.

this is roughly 2 cc per inspiration. The average time of 14.6 minutes for the gas to reach the cecum compares fairly well with Magnusson's average of 10 minutes. His method of checking this time by a retained barium enema is probably more accurate. The objection may be raised that the enema might have increased intestinal peristalsis, but the Levine tube in the esophagus and the rectal tube might also have done the same thing. To avoid this possible irritation it is suggested that a small amount of radioactive argon gas be added to air injected into the stomach and its time appearance at the cecum and rectum determined by a Geiger counter.

The average time for the appearance of flatus was 24.1 minutes, which compares well with Magnusson's average of 30 minutes and is tremendously fast compared to the barium average of 18 to 24 hours. The average volume of flatus passed, 970.8 cc in 83.6 minutes, was very close to the average of 1133 cc of air aspirated.

This experiment corroborates Magnusson's finding on the rapid passage of ingested air through the gastro-intestinal tract, and accounts for gas

TABLE III—*Summary of Data on the Rapid Passage of Air Through the Gastro-intestinal Tract*

Subject and Age		Total Time Exp Min	Air Aspirated Into Esophagus Cc Min		Approx Time to Cecum Min.	Flatus		
						First App Min	Volume Passed Cc	Time Passed Min
NC	23	25	550	08		22		
WH(1)	24	35	1650	30		24		
WH(2)	24	125	2000	37	8	17		
SC	24	64	1000	21		17	1025	47
RS	29	115	1000	33	16	25	600†	91
LS(1)	23	165	1000	28	15	30	600†	135
LS(2)	23	120	*1000	28	18	36	800	74
VT(1)†	28	105	1000	60	20	25	1150	70
VT(2)†	28	144	1000	29	12	19	1450	125
Average			1133	30.4	14.6	24.1	970.8	83.6

* 100 percent oxygen aspirated from spirometer instead of air

† 0.25 mg of prostigmine methyl sulfate given subcutaneously immediately before experiment began and after 1000 cc of flatus had been passed

‡ Rectal tube clogged and flatus collection incomplete

analyses showing the composition of intestinal gas to approximate with some reasonable modifications the composition of atmospheric air.

It is felt that a further investigation of air passage should be done when food or barium is taken at the same time. Patients with ileostomies, cecostomies and colostomies could also be used as a check on the rapid passage of air. The influence of prostigmine and other drugs should be studied further.

METEORISM DURING PYELOGRAPHY

From the results of the previous study it is evident that gas seen roentgenographically in the ileum and colon may have entered the esophagus 10 to 20 minutes previously, and its possible origin as external air should be remembered. The authors considered the accumulation of gas in the intestines

during pyelography as an example of the aspiration and quick transit of external air through the upper alimentary tract, and set out to prove the point.

The study of gastro-intestinal gas in patients undergoing intravenous or retrograde pyelography is a very appropriate experiment in many ways. The time period is short, about an hour. The increased amount of gas seen in many routine pyelographies is sufficient in amount to be measurable. The patient undergoes several possible uncomfortable and strange procedures which may be quite disturbing. With retrograde examination the urethra, bladder, ureters and renal pelvis are stimulated, a procedure often observed to be associated with and resulting in increased intestinal gas, even though there is no pain.¹⁵ If one were to specify the conditions of the whole experiment they would be little different than the routine of a pyelography.

GASTRIC GAS ASPIRATED DURING RETROGRADE PYELOGRAM

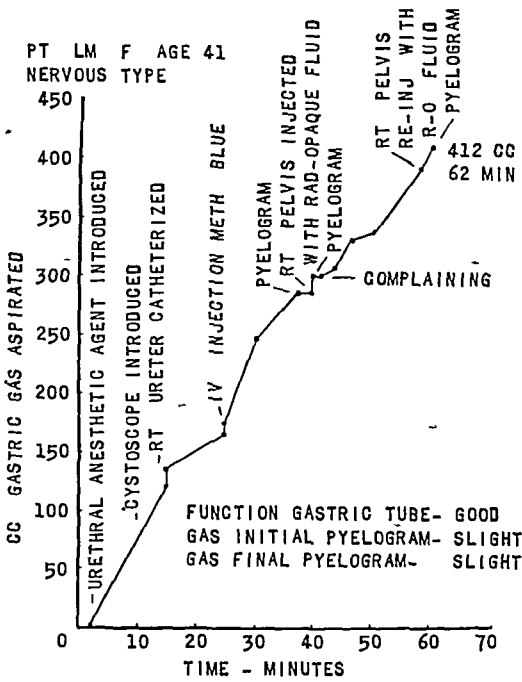


FIG 8—Record of gastric gas aspirated during retrograde pyelography in a nervous patient, L M. Note the sharply increased gaseous return when the right ureter was catheterized, methylene blue was injected intravenously and the right renal pelvis was injected with the radio-opaque fluid. Respirations were increased in rate and depth at these times. Even roentgenographic exposures elicited a response.

pyelography, swallowing movements, complaints of the patient, changes in the rate and depth of respirations and any other emotional reaction. The pyelograms were utilized to determine the effectiveness of the gastric suction in keeping the stomach free of air.

Results Fig 8 shows a typical response in a nervous patient undergoing

* This part of the study assisted by Dr Earl Barth, and Dr V J O'Connor, Prof and Chairman of the Dept of Urology, Northwestern University Medical School

retrograde pyelography In 62 minutes a total of 412 cc of gas, roughly 7 cc per minute, was aspirated from the stomach, and the process seemed definitely related to deeper and irregular respirations as nervous responses associated with the various procedures done, such as the passage of the cystoscope, etc Of special interest was the fact that the stomach was kept empty of air and consequently there was no increase in intestinal gas from the initial to the final pyelogram This is shown in Fig 9 There is no evidence that the various procedures of the pyelography produced atony of the bowel and consequent expansion of gas already present, as suggested by Oppenheimer,¹⁵ or rapid diffusion of nitrogen into the bowel, as theorized by Begg¹⁶

A second typical result in a nervous patient undergoing intravenous pyelography is shown in Fig 10 This man had a total of 1345 cc of gastric gas return in 64 minutes or roughly 20 cc per minute, which is the largest

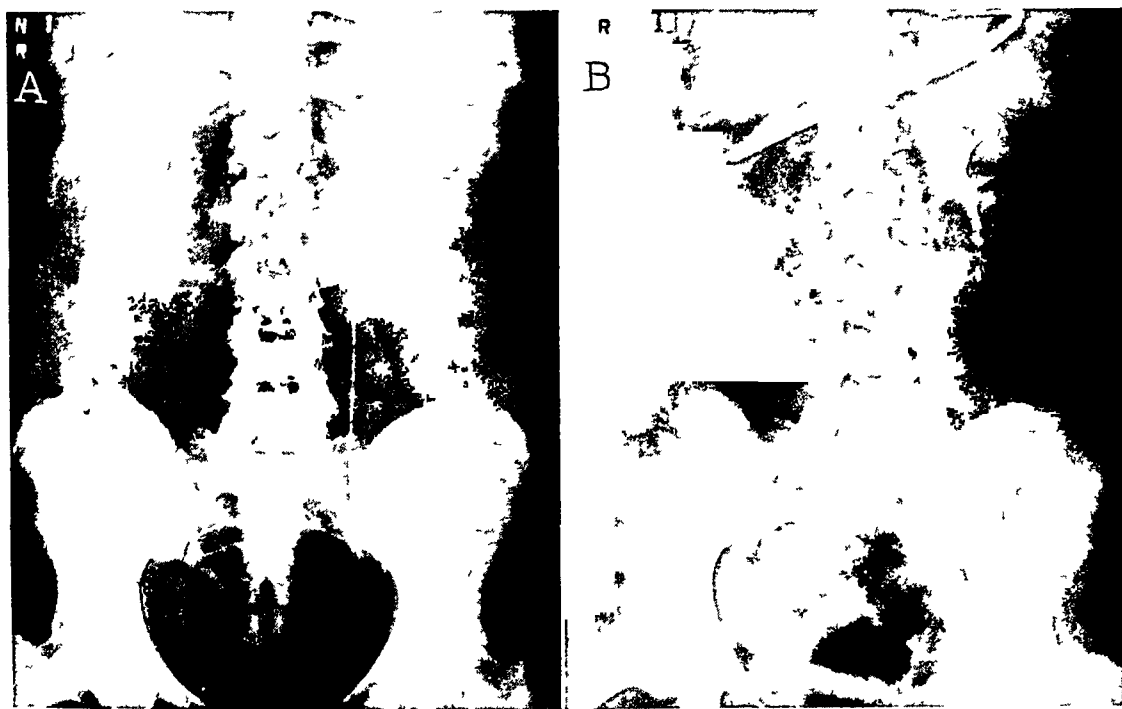


FIG 9—Roentgenograms of patient, L M, who had 412 cc of gastric gas aspirated during the 62 minutes of the retrograde pyelography No increase in intestinal gas from the initial "A" to the final "B" roentgenogram because the stomach was kept empty of air

amount obtained from the group studied He swallowed infrequently, there was no visible air-sucking, aerophagy or belching, yet a steady amount of air passed down the esophagus and was aspirated from the stomach during the disturbing period of the pyelography

From the summarized data in Table 4 the following comments are most pertinent

The time period of study varied from 35 to 68 minutes and the volume of gastric gas aspirated from 45 to 1345 cc The age and the sex of the patients seemed to make no difference Outstanding was the fact that when

the stomach was kept empty of gas by good function of the gastric tube there was no increase in the amount of intestinal gas from the initial to the final pyelogram. If diffusion or fermentation were important sources of gas in these cases this would not be true. The evidence is that gas seen in routine pyelograms comes from external air.

An analysis of the gas returned from patient J. M. undergoing pyelography, and subject V. T. was as follows:

	CO ₂	O ₂	N
J. M. (I. V. pyelography)	1.70%	19.53%	78.80%
V. T. * (Deep breathing)	7.57%	17.08%	75.40%
V. T. † (Air sucking)	1.45%	19.46%	79.09%
City air	0.10%	20.85%	79.05%

V. T. 20 min. deep breathing—270 cc
V. T. † 2 min. air sucking—700 cc

J. M.'s concentrations are quite close to that of atmospheric air and compare well with the sample from V. T. who took in air by deep breathing and air-sucking. The higher values for carbon dioxides are possibly due to the known rather rapid diffusion of this gas into the stomach.¹⁸ Further gas analyses are being planned in a continuation of these studies.

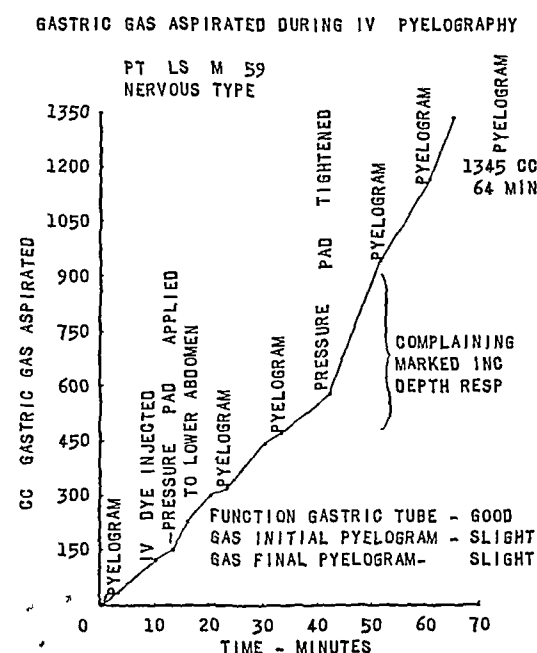


FIG 10—Record of the largest amount of gastric gas aspirated during a pyelography. L. S. was a very nervous patient. As noted for patient L. M. of Fig. 8, the various stimuli from the procedures carried out resulted in a marked increase in the depth and rate of respirations. This was accompanied by the most rapid gas return, the amounts aspirated per deep breath or swallow being greatest with this patient, averaging close to 5 cc. The discomfort from the lower abdominal pressure pad was the most disturbing factor.

When the function of the gastric tube by the observation of M. T. was only fair (two cases) or poor (five cases) there was an increase in gastro-intestinal gas from the initial to the final pyelogram. This (shown in Table 4) is indirect evidence that such gas comes from the outside, because it was there through failure to keep the stomach empty.

An important observation was that three times as much gas returned from the nervous patients than from the calm ones, the averages of Table 4 showing this distinctly, with no material variation whether the patients were undergoing intravenous or retrograde pyelography. This nervous factor is apparent in many observations on air entering the gastro-intestinal tract. Small amounts of gas were aspirated from the calm patients under even normal respirations and more with their few episodes of deeper respira-

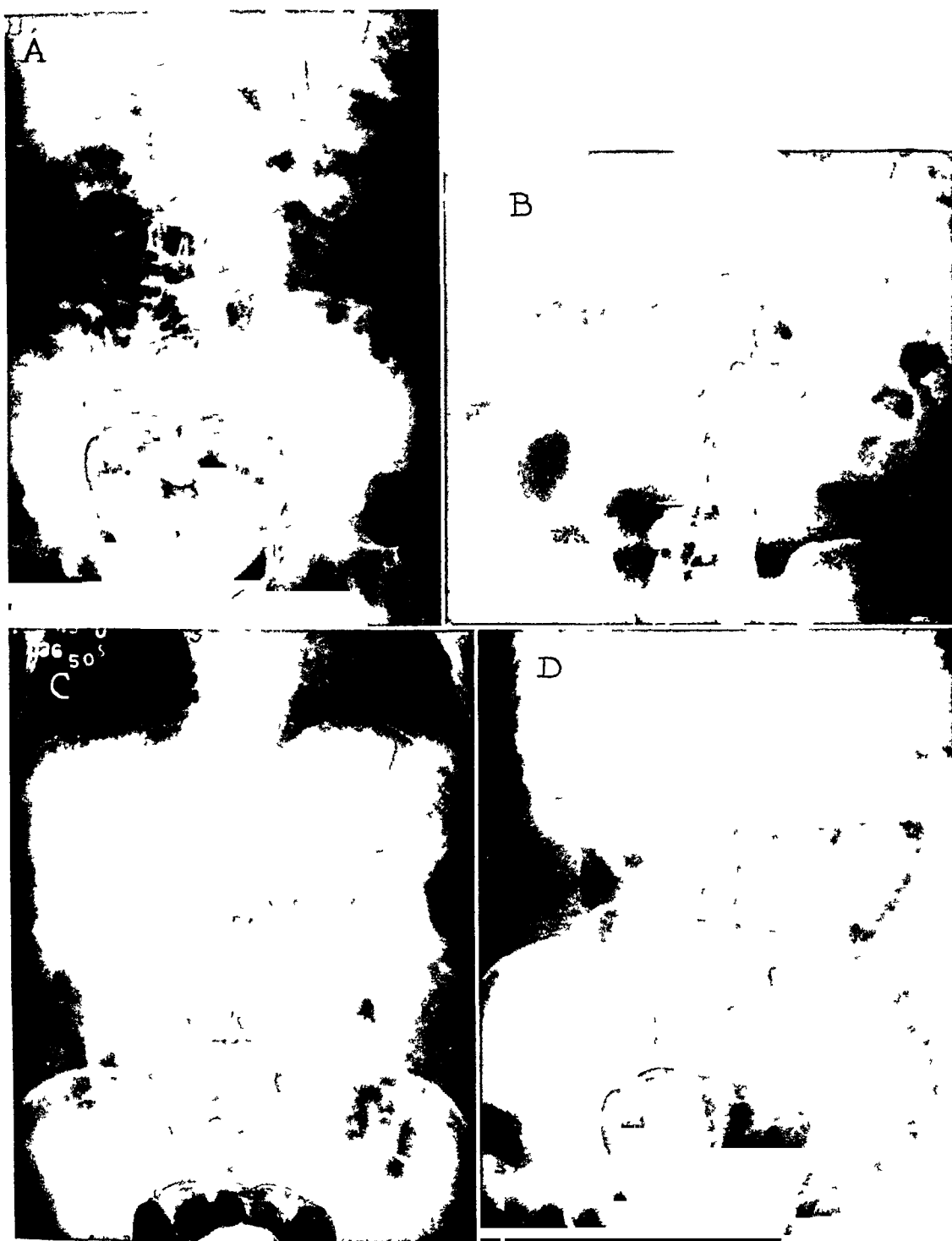


FIG 11—Roentgenograms of nervous patient, L S, who had 1345 cc of gastric gas aspirated during the 64 minutes of the intravenous pyelography (A) The initial film, just after the Levine tube had been inserted, shows a moderate amount of gas in the stomach and intestines (B) Twenty minutes after the intravenous dye injection, 460 cc of gas aspirated. At least the stomach is empty (C) Fifty minutes after the dye injection, 1175 cc of gas aspirated. Intestinal gas seems a little less than in A and B (D) Sixty minutes after the dye injection a total of 1345 cc of gas had been aspirated. Six minutes before this film was taken the gastric tube was removed and gas is now seen in the stomach. The rapid ingestion of air is evident.

tions The nervous patients were much more distressed, had longer periods of deeper breathing and consequently took in much more air Two patients, E S and R J, were addicted to frequent unconscious swallowing This became pronounced during periods of distress and was likely responsible for much of the gas collected The others by request were able to control the act of swallowing and in them this occurred too infrequently to account for any appreciable portion of the gas obtained

The volume of gaseous return following a single swallow varied from 0.3 to 5.0 cc, averaging from 2 to 3 cc Amounts of gas returned with one deep breath varied from 0 to 5 cc, averaging from 1 to 2 cc A respiratory rate of 20 per minute gave plenty of opportunity to take in considerable air

TABLE IV—*Summary of Data on Gastric Gas Aspirated from Patients Undergoing Pyelography*

Subject Sex and Age			Reaction of Patient	Gastric Gas Aspir		Estimation of G I Gas On Pyelogram		Function Gastric Tube
				Min	Cc	Initial	Final	
Intravenous Procedure								
JW	M	53	Calm	61	100	Slight	Slight	Good
SB	F	68	Calm	62	105	Slight	Slight	Good
CB	F	44	Calm	52	195	Slight	Slight	Good
JA	M	51	Calm	46	45	Slight	Moderate	Poor
CS	F	42	Calm	61	165	Moderate	Moderate	Poor
FS	F	66	Nervous	37	165	Slight	Slight	Good
ME	F	53	Nervous	35	195	Slight	Slight	Good
RL	M	15	Nervous	44	200	Slight	Slight	Good
LW	F	43	Nervous	41	240	Slight	Slight	Good
LS	M	59	Nervous	64	1345	Slight	Slight	Good
PR	F	66	Nervous	68	280	Moderate	Moderate	Fair
RJ	M	23	Nervous	53	415	Moderate	Moderate	Fair
RB	F	18	Nervous	48	75	Slight	Moderate	Poor
ES	F	66	Nervous	50	175	Slight	Moderate	Poor
Average Calm Group				56	122			
Average Nervous								
Group				49	343			
Retrograde Procedure								
DB	F	38	Calm	60	55	Slight	Slight	Good
MR	F	47	Calm	56	115	Slight	Slight	Good
WB	F	72	Nervous	40	225	Slight	Slight	Good
LM	F	41	Nervous	62	412	Slight	Slight	Good
PD	F	66	Nervous	45	90	Slight	Moderate	Poor
Average Calm Group				58	85			
Average Nervous								
Group				49	242			

Important Findings 1 Approximately three times more air aspirated from the stomachs of nervous patients than from the calm ones 2 When the stomach was kept free of air by continuous suction through the gastric tube there was no increase in intestinal gas from the initial to the final pyelogram

SUMMARY

There is nothing new in the idea that external air enters the esophagus under many conditions and is the major source of gastro-intestinal gas It appears in the upper alimentary tract of infants within 15 minutes after birth¹⁹ and the roentgenographic findings of air in the bowel has been suggested as a test for extra-uterine life²⁰

Normally the superior esophageal sphincter keeps the esophagus closed. With swallowing movements the sphincter relaxes and air enters with fluid and food. In the upright position the air collects at the top of the stomach, and when more than the usual amount accumulates, as with a meal, it is belched up. Alvarez² remarked that hundreds of patients can be examined with the fluoroscope before finding one with enough air in the stomach to be worthy of special comment.

Excessive amounts of air may enter the stomach by frequent swallowing, and also by the following methods which are variations of the same procedure. The air-sucker can consciously relax the superior esophageal sphincter and by attempting to breathe against a closed glottis can inspire or aspirate air into the esophagus, from which it passes into the stomach. The aerophagic is a nervous individual who unconsciously does the same thing and usually must be convinced of what he is doing to be cured of the habit. The laryngectomized patient can learn esophageal speech with air aspirated into the esophagus by the same method as that of the air-sucker. With skill his aspirations occur with almost normal inspirations and are practically unnoticeable. The repeated belcher takes air into the esophagus to belch with by the same method as the air-sucker, and some can say a few words with the eructated air in the same manner as the esophageal speech patient.

This study has shown that appreciable volumes of air enter the stomach by repeated belching. In the upright position the air is trapped in the cardia and nothing more disturbing than further eructations result, but when lying in bed the air may pass on and cause trouble. A patient with marked gastrointestinal distention from repeated belching is reported.

Patients undergoing anesthesia and operation were found to swallow infrequently, and little gas was aspirated from the stomach of the majority studied. One patient breathing against a partially obstructed airway took in a large amount of air during the operation. This is essentially inspiring against a closed glottis, as done by the air-sucker, and some relaxation of the superior esophageal sphincter by the anesthetic probably played a part. Considerable gas was aspirated from the stomachs of five patients during an operation under cyclopropane anesthesia plus curare. Each was considered to have a partial paralysis of the respiratory muscles due to the curare and positive pressure anesthesia was used. With curare the superior esophageal sphincter was probably well relaxed and the positive pressure forced gas into the stomach.

A rare case of massive, spontaneous pneumoperitoneum is reported. This resulted from perforation of the stomach which became tremendously dilated during a minor operation under sodium pentothal anesthesia. Those in the operating room heard the air entering the esophagus with each inspiration.

Air was found to pass very rapidly through the gastro-intestinal tract. Volumes aspirated into the stomach of experimental subjects reached the cecum in an average of 14.6 minutes and was passed as flatus in 30 minutes.

Oxygen passed along in the same rapid manner. It is evident that gas seen in the intestines on a roentgenogram may be largely atmospheric air which was aspirated esophageally a few minutes previously.

An excellent opportunity for studying rapid accumulations of intestinal gas was offered by patients undergoing pyelography. By continuous gastric suction considerable volumes of air were aspirated from the stomach, and when it was kept empty no increase in intestinal gas occurred. This is further evidence that external air is a major source of gastro-intestinal gas.

The nervous patients undergoing pyelography had three times as much air aspirated from their stomachs as the calm patients. The nervous manifestations were elicited mainly by intravenous injections, the passage of the cystoscope and ureteral catheters, the introduction of fluid into the renal pelvis, and the discomfort of the lower abdominal pressure pad. These stimuli resulted in increases in the depth of respiration, and the gas return was greatest during these periods. A previous study of normal subjects showed that increased depth of respirations increased negative intra-esophageal pressure, and consequently the rate of aspiration of air into the esophagus.

The finding that continuous gastric suction prevented the meteorism of pyelography is the same as continuous gastric suction preventing post-operative distention. Under both conditions considerable volumes of atmospheric air must enter the esophagus and stomach. We consider many patients thus become "temporary aerophagics," using the word in a broad sense. Marked aerophagia is usually a readily apparent, nervous phenomenon, but it can be a less evident process such as used by the esophageal speech expert. There is every reason to believe that patients under many conditions become temporary aerophagics and the stimulus may be entirely nervous without organic origin or be associated with an organic disease or injury and its treatment.

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DISCUSSION—DR WILLIS D GATCH, Indianapolis, Ind This fascinating work of Dr Maddock and his associates is of great clinical value The ingestion of air is a common cause of symptoms diagnosed as gallbladder disease, ulcer, appendicitis, etc A careful history will in most cases determine the diagnosis

I have shown that extreme dilatation of the stomach of a dog will kill it in about two hours by asphyxia I have observed acute dilatation of the stomach occur suddenly in hysterical patients I remember two of these who would certainly have died had their stomachs not been deflated

Air ingestion is, I think, an occasional cause of death under anesthesia

I fully believe in what Dr Maddock has said about the mechanism by which air gets into the esophagus, but I believe another mechanism acts in some cases Perhaps Dr Maddock has discussed this in his paper submitted for publication

I derived by inference the following ideas from an article by Sir Arthur Keith published in 1913 in the British Journal of Anatomy and Physiology This gives the best account I have ever found of the evolution of the diaphragm and its relation to the mammalian lungs In the reptiles the lungs are in the abdomen The great activity of which these creatures are capable proves that they must have a very efficient respiration such as could be carried on only by the continuous alternation of negative and positive pressure within the abdomen

I believe that when the following events occur a negative intraabdominal pressure may be produced in man

- 1 Contraction of the abdominal muscles
- 2 Relaxation of the diaphragm (The abdomen and chest then become a single cavity as far as pressure is concerned)
- 3 Elevation of the ribs (Under these conditions this creates a negative pressure in the abdomen)
- 4 Relaxation of the superior sphincter of the esophagus

A great quantity of air can then rush into the stomach Some men can voluntarily perform these acts This explains, I think, the trick of downing a bottle of beer at one gulp

DR JOHN RANDOLPH PAINE, Buffalo, N Y Gentlemen, I believe Dr Maddock has shown us very well how in many of our patients troublesome accumulations of gas occur, yet to my mind why these patients get gas accumulation seems a little mysterious

To say that it is on some type of a nervous or psychogenic basis does not entirely satisfy me It might be that some of us have received the impression that we need a psychiatrist to take care of the situation

It would be nice, I think, if we could say beforehand that this patient will not be troubled with distention after operation, that this other patient will be so troubled, but I don't believe many or any of us can do that I say this because, despite the fact that a surgeon in a small midwestern city once said that the institution of gastric duodenal intubation had made a civilized business out of abdominal surgery, still the more or less routine institution of gastric duodenal aspiration is not certainly all we might like to have it Many of our patients complain of the discomfort of the tube and usually the highstrung, nervous patient who complains is the very one who needs it most

I think it is very evident that there are two elements here, one, a somewhat active element in which the patient, by swallowing air or air sucking, actively forces air into his stomach, but there is another element, another more or less passive element, in which by the rhythmic change of pressure in the chest, with respiration, air is pulled into the esophagus to be passed on down into the stomach

I think these studies can be followed further with a great deal of profit There would be two things I would be particularly interested in One thing in which I am interested is to note what, if any, effect there is on accumulation of air in the gastrointestinal tract from the ingestion of various types of food All of us know that certain types of food bother us more than other types

Another thing is the question of why we don't have as much trouble as we might think we would have in patients in whom the stomach has been more or less denervated and pulled up into the chest One would think if air were aspirated into the esophagus it could be aspirated as well into the stomach, and we should have a great deal of trouble with patients after esophageal resections, yet in my experience, somewhat limited, to be sure, trouble of this nature has not been very great

However, some experiments in dogs leads me to think that occasionally this is a very serious problem At numerous times we have denervated the stomach freely from its attachment in the abdomen and pulled it into the chest Most of those dogs die within two weeks, some of them die within two or three days and some within 24 hours from an acute dilatation of the stomach I have seen one dog go as long as six weeks, be perfectly all right, and within five minutes after apparently being perfectly all right, be dead At autopsy the chest was opened and the stomach was tremendously distended with gas

These accumulations can occur from some mysterious cause, as far as I know, in a very short time

DR WALTER G MADDOCK, Chicago I wish to thank Drs Gatch and Paine for their remarks They have long been interested in abdominal distention and their suggestions will be investigated

We have planned considerably more work on this problem We know that in allergy patients certain foods will cause rapid distention, and such a phenomenon offers an excellent opportunity to learn more of the mechanism of gas entrance into the upper gastro-intestinal tract We have been impressed by the nervous element in many instances of gastro-intestinal distention For instance, during pyelography the amount of gas taken in by the nervous patients was three times more than for the calm patients Surgeons have occasionally been able to predict a stormy postoperative course because a patient was extremely nervous and apprehensive, and therefore was

easily upset by the operation and subsequent care, was unable to void and developed marked gaseous distention, all leading to a poor convalescence

In regard to the rapid passage of air through the gastro-intestinal tract we believe the studies should be repeated when food or barium are taken at the same time as the air. This may not be important clinically because many patients during the period of distention are eating lightly or not at all. The effect of various drugs on the rapid passage of air should also be investigated. I would like to add a radio-active gas as a marker for the passage of air through the alimentary canal. Further information on the time of passage might be obtained, and in tune with the times, all modern experiments employ a radio-active substance and a Geiger counter.

Dr Paine's observations on patients whose stomach has been brought up into the chest and his work on dogs along this line are interesting. Considering the possibilities of negative intra-gastric pressure from thoracic respiratory movements these patients should certainly have some trouble. Dr Richard Sweet's observations are the same as Dr Paine's in that during the immediate postoperative period there is often some distention, but this subsides in a few days' time.

Dr Gatch's remarks about the men who can drink a bottle of beer without swallowing are pertinent because these individuals are examples of those who can voluntarily open the superior esophageal constrictor without swallowing. I would like to call on one of my co-authors to come up here for a moment. He can voluntarily relax the superior esophageal sphincter and will give a demonstration of air sucking and belching. Notice how he moves the chin forward as part of the process of relaxing the sphincter. Then by attempting to draw in a breath against a closed glottis he is able to aspirate air into the esophagus, and a good belch follows.

I am sure the members of this organization have seen many instances of distention occurring with grunting or exaggerated respirations from a variety of causes. We well know that the effects of distention are serious and often are lethal. It is fortunate that we have learned the value of continuous gastric suction and one cannot over-emphasize that our efforts should be directed towards preventing distention rather than having to treat it after it has occurred.

SPHINCTER PRESERVING OPERATIONS FOR RECTAL CARCINOMA AS RELATED TO THE ANATOMY OF THE LYMPHATICS*

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AND

JAMES B BLAIR, M D (By invitation)

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ALL SURGEONS interested in the management of carcinoma of the rectum, rectosigmoid and lower sigmoid are mindful of a slowly changing trend from the radical abdominoperineal resection with complete extirpation of the sphincter apparatus to a radical procedure with preservation of the sphincter mechanism. This is a revival of the ambition of all the early surgeons who conservatively removed the malignant growth but saved the posterior stoma of the gastrointestinal tract with hopes of proper control of this orifice. Because of our unending efforts to improve the management of disturbances of the human body, the pendulums of thought and action keep swinging, usually toward progress and better goals. Occasionally something entirely new makes its appearance, but more frequently the new thought or mode of execution is an elaboration and popularization of material introduced by our predecessors. Usually, with each revival, something constructive evolves, the pattern of management or treatment may change in entirety or only in part, or it may possibly retain the status quo.

Today we are fervently discussing all the aspects of the proper treatment of carcinoma of the rectal and rectosigmoidal areas. Some hesitate to return to a discussion of any operative procedure which entails an attempt to preserve the sphincter mechanism because of the poor results experienced prior to the introduction of the popular radical abdominoperineal procedure (so-called Miles operation) of the last 25 years. However, we must not forget that some of the same forces which have worked to improve our results with this procedure may also be of assistance in some slightly less radical procedure which does not destroy the controlling outlet of the lower intestinal tract.

Usually our discussions deal with the local anatomy of the lymphatics. However, other factors must be considered when one discusses recurrence of malignant growths. Carcinoma spreads by direct extension, by venous channels, by the lymphatic channels and by transplantation, and all these avenues of spread should be kept in mind when considering recurrence of rectal carcinoma following various operative procedures.

Our surgical principles for removal of malignant growths demand that we excise widely from the palpable tumor margins. In carcinoma of the rectum, the intramural spread or extension downward in the rectal wall has been

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investigated frequently, and it is most unusual to find tumor cells $2\frac{1}{2}$ cm (1 inch) below the palpable tumor margin. One is referred to the studies of McVay,¹⁸ Gilchrist and David¹⁴ and Collier, Kay and McIntyre¹⁰. Thus, if one transects the rectum 4 to 5 cm ($1\frac{1}{2}$ to 2 inches) below the palpable tumor margin, there need be little fear of local recurrence from this factor.

The dissemination of cancer cells through the blood stream does occur, but references to this in the literature are relatively few. Perhaps more emphasis should be placed on this potentiality. In carcinoma of the rectum, the findings of inoperability and recurrence are most frequently coincident with the presence of malignant cells in the liver or in the general peritoneal cavity. Again, not infrequently, we find a relatively small rectal lesion, or a large rectal lesion with no involvement of adjacent lymph nodes, and yet we discover diffuse metastatic nodules in the liver. The route of vein invasion of small tributaries of the portal system and dissemination in the liver is certainly more direct than the passage through lymph channels, the thoracic duct, and then into the general venous circulation. Brown and Warren⁸ found vein invasion in 61 per cent of 165 autopsies on patients with rectal carcinoma. Grinnell,¹⁷ in a series of 75 fresh surgical specimens of carcinoma of the rectum, found the incidence of blood vessel invasion to be 36 per cent. One cannot help but be impressed by those instances where there is no macroscopic or microscopic evidence of lymph node involvement and yet signs of early recurrence are ushered in by liver metastasis. It is doubtful that removal of a sphincter area which is a reasonable distance below the tumor margin would alter the percentage of recurrences if vein invasion is a factor. This danger would be centripetal.

Since so much has been written on spread of carcinoma through the lymphatics, and such great emphasis has been placed on the radical excision of tissues above and lateral to the tumor and even on excision of the remaining anus and rectum to conform to the principles of the Miles procedure in carcinoma of the rectum, a careful review and careful analysis of all the facts should be made. The anatomy of the lymphatics has not changed but our concept of the mechanics or physiology may change. There is no controversy about the zone of upward spread but the zones of downward and lateral spread should be re-evaluated.

Unfortunately, little attention was given to the report of McVay¹⁸ in 1922 on the involvement of lymph nodes in 100 cases of carcinoma of the rectum. Although 47 had metastasis to lymph nodes, in only one case was there involvement of a lymph node below the lower margin of the lesion, and this was at the 1 cm distance. Since then other reports on node involvement below the lower margin of a tumor have been made by Wood and Wilkie²¹ in 1933, Westhuer²⁰ in 1934, Gabriel, Dukes and Bussey¹³ in 1935, Gilchrist and David¹⁴ in 1938, Collier, Kay and McIntyre¹⁰ in 1940, Grinnell¹⁷ in 1942, and Glover and Waugh¹⁶ in 1944. In analyzing the reports on downward spread we find only five cases (8 per cent) of the total of 607 cases reported in which there was

lymph node involvement more than 2 cm below the lower margin of the tumor (Table I). The significance of this low percentage as balanced against the number of patients in this group who actually died of recurrent cancer within the five year period cannot be denied. In this latter group, an estimate of 200 or approximately 33 $\frac{1}{3}$ per cent would be conservative. At this time, and from these figures, one cannot authoritatively debate that transection of the rectum 5 cm (2 inches) below the lower margin of the lesion following radical excision above and lateral to the incision would have seriously altered the percentage of cures. It is possible that actual experience may at some time prove, because of factors unknown at this time, that it is more feasible to remove the anorectal segment. Such evidence is not available at this time under modern surgical conditions and technique.

TABLE I—*Collected Data on Incidence of Lymph Node Involvement Below Margins of Malignant Lesions*

Author	Year	Cases Studied	Cases with Nodes	Cases with Nodes
			(1 to 2 cm below lesion)	(2 cm or more below lesion)
McVay	1922	100	1	0
Wood and Wilkie	1933	100	0	0
Westhuer	1934	74	1	0
Gabriel, Dukes and Bussey	1935	100	2	0
Gilchrist and David	1938	25	0	2
Collar, Kay and MacIntyre	1940	33	1	0
Grinnell	1942	75	1	0
Glover and Waugh	1944	100	6	3
Total cases		607	12	5
Percentage			2.3	.82

Lateral spread is a factor which probably is not so clearly understood because it is possible that our surgical specimens have not been excised widely enough in this direction and thereby are not permitting a true analysis. This must be particularly true in lesions of the mid- and lower rectum adjacent to the levator ani structures. Gilchrist and David¹⁴ noted lateral spread in four of 47 surgical specimens, or 8.5 per cent. Coller, Kay and MacIntyre¹⁰ found lateral spread in six of 53 surgical specimens, or 11.3 per cent. Because of this rather vague understanding of the lymphatics of the levator ani muscle and fascia and the lymphatics above and below the levator ani muscle, a study of these structures was undertaken several years ago. After preliminary experimentation with various substances to demonstrate lymphatic patterns, the one we chose to use most frequently was India ink neutralized to pH 7.2 with N/10 hydrochloric acid suspended in an equal volume of isotonic saline. A 2 cc syringe with a 27-gauge needle served as the instrument for injecting the dye material into the lymphatics. The dye was injected slowly under constant minimal pressure and the quantity used never exceeded 0.2 cc in any given area of tissue. The first studies were made in animals and final studies

were completed on 15 stillborn fetuses. The details of the experiments are being reported in a thesis on the subject.⁷

After a careful review of previous studies on this subject and a careful analysis of our material, we have in our own minds crystallized the pattern for the lymphatics of the anorectal area with particular reference to the anal canal and the rectum adjacent to the levator ani muscle. There is a lymphatic network in the perianal skin, including the lower anal canal to the level of the mucocutaneous junction, and another lymphatic network in the remaining anorectal mucosa and rectal wall structures. These lymphatic plexuses are drained by three groups of efferent channels identified as the inferior, middle and superior channels draining corresponding areas of the anorectal canal (Fig 1).

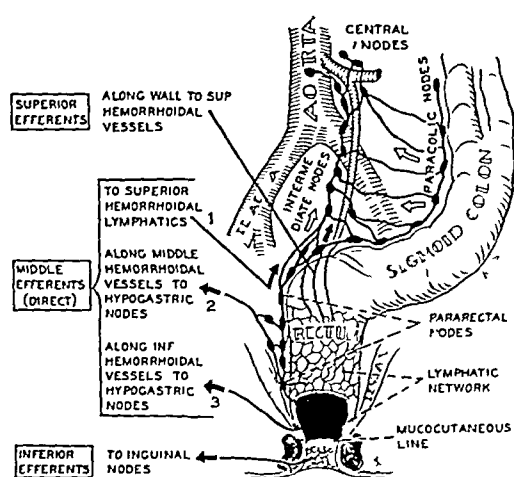


FIG 1

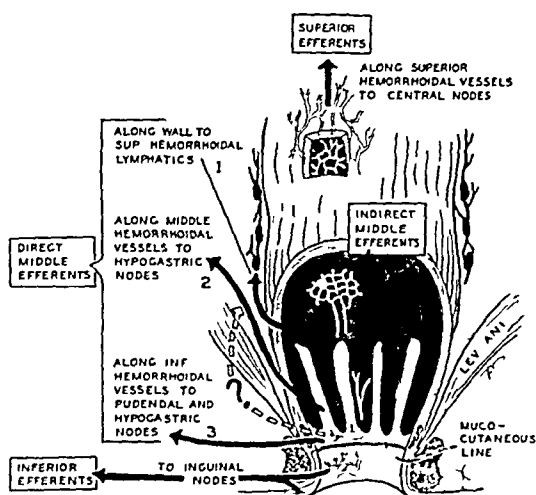


FIG 2

FIG 1—Diagram of the lymphatic pattern for the anus, rectum, and rectosigmoid region

FIG 2—A more detailed diagram of the lymphatics of the mid and lower rectal region, *ie*, that segment of rectal wall adjacent to the levator ani muscles

The inferior efferent channels drain the immediate perianal region and the anal canal to the level of the mucocutaneous line. Frequently two or three small efferent lymphatic channels were demonstrated on either side leading along the perineum or medial aspect of the thigh and emptying into the superficial inguinal lymph nodes. From this study it would be interpreted that with an epithelioma in the perianal region which did not involve the true anal canal lymphatic spread would occur only to the inguinal lymph nodes. Treatment with radium would probably suffice, although radiation or inguinal lymph node dissection should be considered. If the lesion is definitely within the anal canal and below the mucocutaneous line, similar management might be adequate, as our studies did not reveal communicating channels between the inferior and middle groups of lymphatics at the level of the mucocutaneous line. However, there is a possibility that the cancer might spread by break-through from the inferior to the middle group of lymphatics and then into the lymphatics on the under or upper surface of the levator ani muscles. With this possibility in

mind, a radical abdomino-perineal excision is indicated, with wide excision of the levator muscles and sacrifice of the sphincter mechanism

The middle efferent channels drain the level at and above the mucocutaneous juncture and to or above the level of the middle hemorrhoidal vessels, particularly that part of the rectum which is attached to or adjacent to the levator ani muscles. These middle efferent channels are divided into the indirect and direct channels. The indirect channels ascend in the columns of Morgagni and continue upward into the lymphatic network of the upper rectal mucosa. The direct channels perforate the wall of the rectal canal and travel in three different directions. (1) Those in Group I are rather inconstant, they correspond to the course of the inferior hemorrhoidal vessels below the levator ani muscle and traverse the ischiorectal fossa, terminating in nodes along the internal pudendal vessels and thence to the hypogastric nodes along the internal iliac. Lymphatic channels perforating the levator ani muscle itself are practically non-existent as evidenced by our injections. In two instances, a single minute lymphatic channel pierced the levator muscle to apparently end in the hypogastric nodes. (2) Group II channels correspond to the course of the middle hemorrhoidal vessels, draining the area of rectum attached to or adjacent to the levator ani muscles. These channels lead to the hypogastric glands along the internal iliac vessels. (3) Group III channels perforate the rectal wall, ascend along the rectal wall into the pararectal nodes and thence upward along the superior hemorrhoidal vessels (Fig 2). Carcinomatous lesions in the area of these middle efferent channels would include those lesions within approximately 10 cm (4 inches) of the external sphincter margin, and above the mucocutaneous line. These lesions have good potentialities for lateral spread, but as previously stated Gilchrist and David¹⁴ reported only 8.5 per cent and Collier, Kay and McIntyre¹⁰ reported only 11.3 per cent from a careful study of fresh surgical specimens.

Balancing the apparent potentialities for lateral spread and the relatively small percentage reported against the general acceptance that lesions of the lower rectum give the poorer prognosis, there should be some attempted explanation. Dukes¹² has expressed the opinion that lesions in the mid-rectal region did less well than similar lesions elsewhere in the rectum because of the tendency of such lesions to grow laterally along the lymphatics accompanying the middle hemorrhoidal vessels. Gilchrist and David¹⁵ in 1947 reported that the five year survival rate for low lying carcinoma of the rectum (below peritoneal reflection) without evidence of gland involvement was 74.4 per cent, while the survival rate for lesions at or just above the peritoneal reflection was 90 per cent. Where nodal metastasis was present, the figures for similarly placed lesions were 37.5 per cent and 51.4 per cent. Waugh and Kirklin¹⁰ in 1949, in a somewhat similar analysis of their cases, reveal a 70.5 per cent five year survival rate in patients where no gland involvement was present and the lesion was below the 10 cm (4 inch) level, and a 68.1 per cent survival rate with lesions at or above the 11 cm level. Here, this difference is not

noticeable. However, when node metastasis was present, the five year survival rate for patients with lesions below the 10 cm level was only 24 per cent and with lesions at or above the 11 cm level, the figure was 33.3 per cent. The latter authors further analyzed the survival rate as related to the level of the lesion and revealed that the survival rate for the region between the 3 to 6 cm level was only 17 per cent if metastasis was present. The lower five year survival rate for these lesions at the lower levels is further suggestive that in the area where the levator ani muscles are most closely associated with the rectum, the problem of complete extirpation of the malignancy is more complicated.

The investigations of Gilchrist and David,¹⁴ who studied fresh surgical specimens, clearing them by a modified Spalteholz technic, were a most careful study, and there was a 62 per cent lymph node involvement in their cases. Waugh and Kirkin¹⁹ studied old uncleared surgical specimens and there was only a 43.2 per cent node involvement, quite possibly their five year survival rate in cases with metastasis would be a little higher if they had examined the specimens in the fresh state by the clearing technic as node structures are better identified. In any event, their figures are of importance and are quite parallel. There is a noticeably poorer prognosis in lesions where the rectum is attached or adjacent to the levator ani muscles, and particularly when lymph node involvement has been demonstrated. From these survival rate figures of other authors for patients with or without lymph node involvement in lesions located above the mucocutaneous line and below the 10 cm level, and from our experimental study of the lymphatics, it would seem that wider extirpation of the levator ani muscles, fascia and adjacent lymphatics is indicated. This cannot be accomplished by an operation where the dissection, resection and anastomosis are accomplished from within the abdomen. The proper procedure for lesions at these levels would appear to be that of abdominal dissection to assure sufficiently high extirpation, followed by posterior dissection and anastomosis to permit radical removal of the levator ani and adjacent structures.

The superior efferent collecting trunks were shown to pass through the muscular coat of the upper rectum and rectosigmoid area and extend backward and upward to reach the pararectal nodes and course upward along the superior hemorrhoidal vessels (Fig. 2). In carcinoma at this level (above 10 cm) where the lesion is not directly adjacent to the levator ani structures, it would appear that transection of the rectum $3\frac{1}{2}$ to 5 cm ($1\frac{1}{2}$ to 2 inches) below the lower margin of the tumor, wide excision laterally but not removing the levator structures, and adequate high transection of the sigmoid to eradicate paracolic nodes, should suffice.

One of us (R. R. B.), over a period of ten years, and only in selected cases, has done a radical excision of carcinoma of the rectosigmoid region with immediate anastomosis of the colon to the rectal stump, and on occasion has anastomosed the ileum to the rectal stump⁶ for carcinoma of the rectosigmoid. Beginning in 1946 in view of various publications on the subject

relative to the lymphatics, direct efforts have been made to preserve the sphincter mechanism if at all feasible, in patients with carcinoma of the lower sigmoid, rectosigmoid or rectum. Of course these sphincter preserving operations were done only when it was felt that a radical eradication of the disease was also being accomplished. The modified pull-through operation of Hochenegg, as advocated by Babcock¹ and Bacon,² was tried a few times, but our experiences were not satisfactory.

Gradually, three different operative procedures were developed^{3,5} and used where it seemed practicable to forego the radical abdomino-perineal excision of Miles and to attempt to preserve the sphincter mechanism. *Operation I* is entirely an abdominal operation, with radical excision of the sigmoid, rectosigmoid, and mid and upper rectum, for lesions at or above the 10 cm (4 inch) level from the external margin of the anal canal, provided one is able to transect the rectum at least $3\frac{1}{2}$ cm below the lower margin of the lesion and effect an end-to-end anastomosis. In some of the earlier cases this operation included lesions 5 cm (2 inches) from the anal sphincter, but with further experience, study and analysis, we felt these lower lesions should be attacked by a combined abdominal-perineal approach. *Operation II* is the combined abdominal-perineal procedure in which the dissection and freeing of the upper zones of spread are done from within the abdomen. Then the patient is turned onto the left side and further dissection and resection and the anastomosis are accomplished through a sacral incision. We now feel this operation is indicated in those lesions between the 5 cm (2 inch) and 10 cm (4 inch) levels. One cannot excise the levator muscle, fascia and the lymphatics on their upper and lower surfaces from within the abdomen, this is only accomplished through the posterior incision. Early in our investigative work on the lymphatics of the levator region, we became conscious that the operation for low and mid-rectal carcinoma was inadequate when executed entirely from within the abdomen and therefore we developed a technic for abdominal dissection, posterior resection and anastomosis. Also, we became more and more conscious that in the Miles operation of radical abdomino-perineal excision we were probably not being sufficiently radical in the excision of the levator muscles and adjacent structures in lesions below the 10 cm level. *Operation III*, perineal dissection, resection and anastomosis, is accomplished entirely through the posterior approach. It is not a fundamentally sound operation for carcinoma of this area because one cannot adequately remove the zone of upward spread. However, it may be the operation of choice in some poor risk patients when the entire lesion is palpable per rectum (i.e. the upper level can be definitely determined), and in some other unusual circumstances. The lower margin of the tumor should be at least $2\frac{1}{2}$ cm (1 inch) above the upper margin of the muscular anal canal. This operation is similar to the Lockhart-Mummery procedure, except that the anus is not removed and an anastomosis is accomplished.

The last cause for recurrence of carcinoma in this region, as mentioned earlier in this paper, deserves some consideration. Carcinoma by transplant, either independently or as a factor in the operative procedure, must occur more frequently than is mentioned in the literature. That this complication occurs in the line of incision for breast carcinoma and in some abdominal incisions is well known. Recently, Chase⁹ emphasized that in operations for cancer of the breast, the carcinoma cells can frequently be found in stained smears made from gloves or instruments or centrifuged sediment from hand basins. The same must hold true when we divide any segment of the gastrointestinal tract. The recovery of malignant cells in this type of study would only be the application of the Papanicolaou principle for diagnosing malignancy in body secretions. This brings up the question of how long these detached

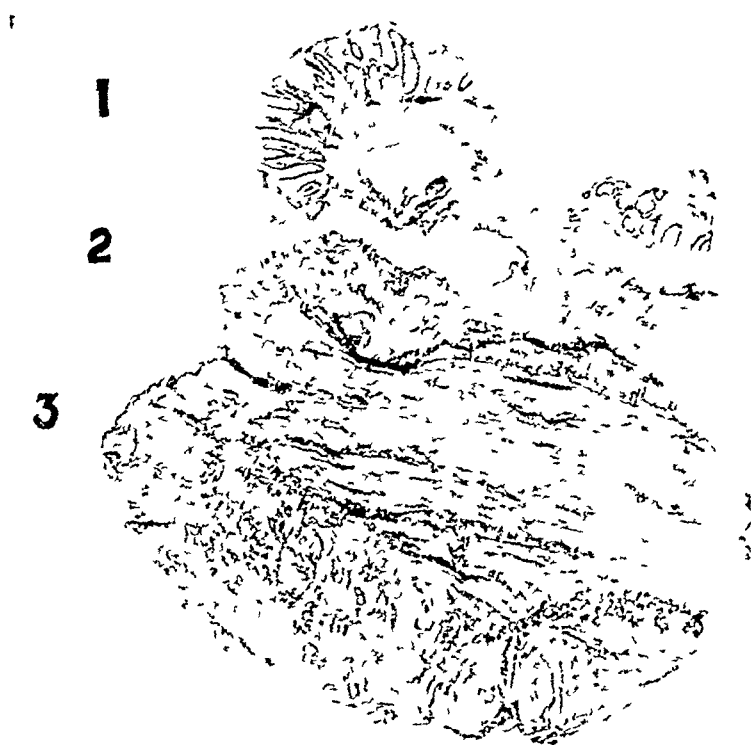


FIG 3—Microscopic section through tumor area in a patient with recurrent carcinoma of the rectum

- 1 Normal mucosa was present
- 2 The muscular layer of rectal wall was normal
- 3 An extrarectal tumor mass of carcinoma was present

carcinoma cells survive. One of us (R R B) has had the opportunity to do an abdomino-perineal resection in one of our patients where recurrence had followed rectosigmoidectomy with anastomosis 13 months previously. In this patient, a mass developed in the hollow of the sacrum and, by palpation and visualization, the mucous membrane of the rectum appeared intact. A radical Miles operation was carried out; the fresh specimen was closely examined microscopically and macroscopically, and it was definitely established that the recurrence was a transplant growing between the sacrum and the rectal wall (Fig 3). In a second case where recurrence was found, the mucosa at the

site of recurrence appeared normal, but at re-operation the lesion proved to be non-resectable and there was no final opportunity to prove or disprove the transplant phenomenon. The question of transplants in this area is of considerable concern to us and it is being further investigated.

In a series of 51 consecutive cases where preservation of the sphincter mechanism was given serious consideration, yet radical eradication of the malignancy was kept foremost in mind, we operated upon 44 patients, an

TABLE II—*Carcinoma of Rectum and Rectosigmoid, Analysis of 51 Consecutive Cases*

	Cases	Operated*	Resected*	Anastomosis†	Abd perineal†
Number	51	44	38	29	9
Percent		86 2%	74 5%	76 3%	23 6%

* Per cent of total cases seen † Per cent of resectable cases

Note The percentage of anastomoses in resectable cases has decreased (88% of first 33 cases reported 83 4% of first 40 cases reported 76 3% of first 51 cases reported)

The remaining resectable cases were treated by abd perineal resection

operability rate of 86 2 per cent. Thirty-eight (74 5 per cent) of these were resectable. In 29 patients, or 76 3 per cent of those resectable, a sphincter preserving operation was accomplished by one of the procedures we have elected to call Operations I, II and III. In nine cases (23 6 per cent), because of the low location of the lesion or some other factor, abdomino-perineal resection was done with sacrifice of the sphincter apparatus. In other words, we preserved the sphincter mechanism in 29 of the 38 resectable lesions (Table II). Among the resectable cases, there were two deaths, a mortality

TABLE III—*Carcinoma of Rectum and Rectosigmoid, Mortality in 51 Consecutive Cases*

	Cases	Operated	Resected	Anastomosis	Abd perineal
Number	51	44	38	29	9
Per cent		86 2%	74 5%	76 3%	23 6%
Deaths		4*	2	2	0
Per cent		9 0%	5 2%	6 8%	0%

* Two of these deaths followed colostomies

rate of 5 2 per cent for the 38 cases. These two deaths occurred in the group of 29 cases where an anastomosis was accomplished, giving a mortality rate of 6 8 per cent for rectosigmoidectomy with anastomosis. There were no deaths among the nine cases of abdomino-perineal resection (Table III).

At the present time, we have data on recurrences in three patients—one who has died and two who were re-operated. I have had the good fortune to re-examine and re-operate on these two patients. In one, the lesion was found to be so infiltrative throughout the pelvis that only a colostomy was done. In the other patient, an abdomino-perineal resection was accomplished.

Although time and further experience may prove some inadequacies of these sphincter preserving operations, one cannot help but be impressed by the probabilities of diagnosing recurrences in the pelvis far earlier than when the abdomino-perineal resection has been done. One is unable to examine ade-

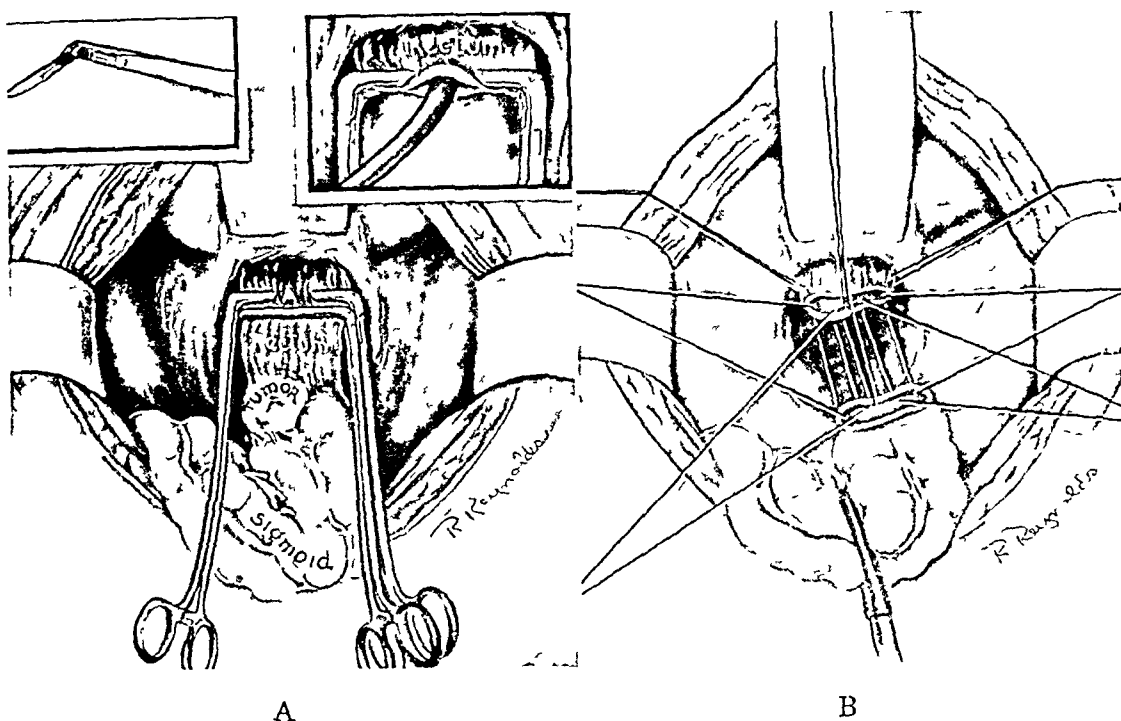


FIG 4—Anterior dissection, resection and anastomosis (A) Special clamps** applied below the tumor mass permit transection at least one inch below the tumor margin Catheter suction introduced into lower segment between clamps removes contents (B) Short nosed lower clamps removed and replaced by guy sutures to steady lower segment Five long posterior catgut guide sutures inserted to direct correct apposition of posterior walls, knots will be on mucosal side

** By V Mueller Company, Chicago, Illinois

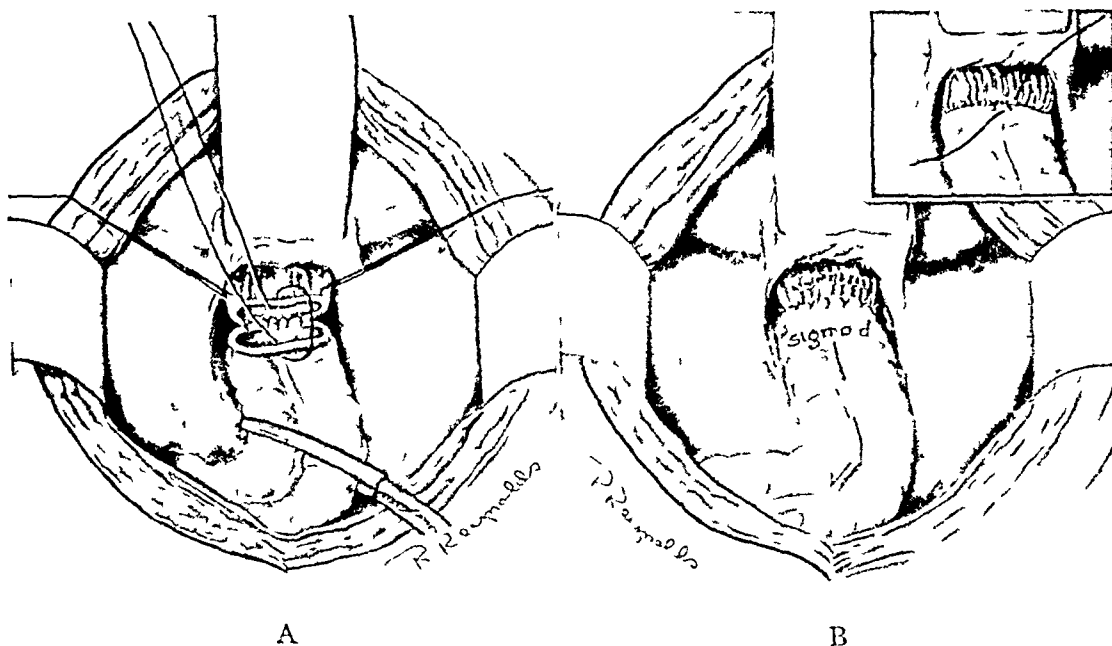


FIG 5—Anterior dissection, resection and anastomosis (A) The five posterior guide and inversion sutures have been tied One similar inversion catgut suture is placed on the anterior wall, knot on mucosal side (B) The anastomosis is completed with a layer of figure of eight silk sutures on anterior and lateral walls and insofar as possible on the posterior wall A penrose drain is placed in the hollow of the sacrum, peritoneum of pelvic floor is sutured over the drain and around the rectum A Gibson type cecostomy is accomplished and after closure of abdomen, the patient is turned on the left side and the drain delivered posteriorly through a small incision alongside the coccyx

quately the site of the original lesion following the Miles procedure, but with an anastomosis, the digital and proctoscopic examinations are still possible, and symptoms are expressed. In the one case where we did an abdomino-perineal resection 13 months following rectosigmoidectomy with anastomosis, the patient is well and active six months postoperatively.

There has not been a sufficient number of cases reported by a sufficient number of surgeons to permit definite conclusions from comparison of five year survival rates of patients who have been treated by radical abdomino-perineal excision and sacrifice of the sphincter, and of those who have had radical

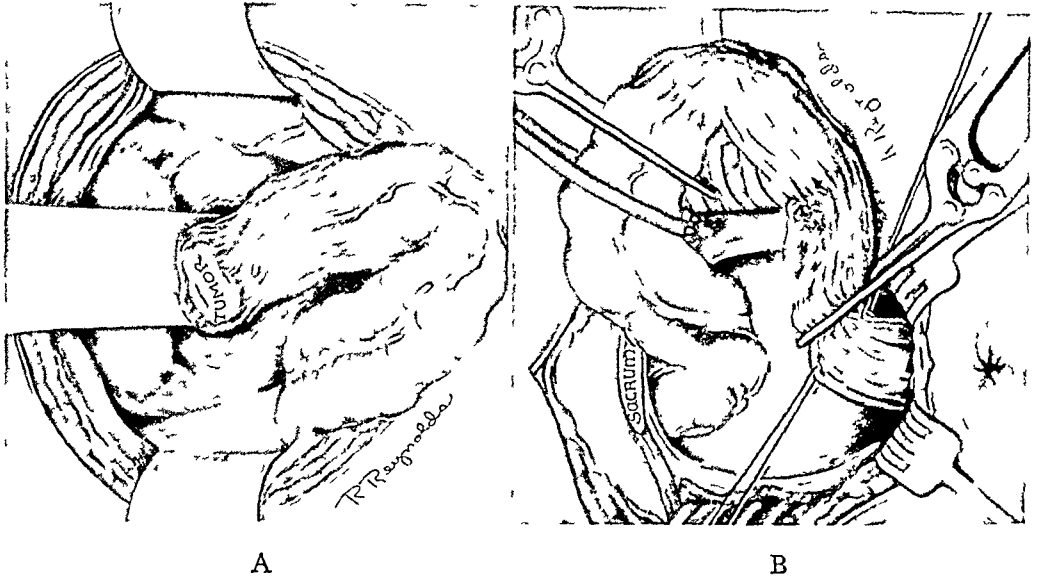


FIG 6—Anterior dissection with posterior resection and anastomosis (A) Through an abdominal incision, pelvic structures have been dissected and freed. The tumor mass which has been freed is replaced in the hollow of the sacrum and the pelvic floor peritoneum sutured around the rectum loosely enough to permit drawing the sigmoid downward through the posterior incision. A Gibson type cecostomy is accomplished and the abdomen closed. (B) With the patient on his left side, an incision has been made along the coccyx and sacrum, coccyx is removed, wide dissection of levator ani structures is accomplished, and the rectum and sigmoid delivered and resected.

rectosigmoidectomy, anastomosis and preservation of the sphincter mechanism. This is particularly true when the lesion is below the rectosigmoid. In 1948, Dixon¹¹ reported to this Association on his experiences with anterior resection and anastomosis in selected cases. The greater percentage of these patients had lesions at the rectosigmoid and upper rectum, although some with lesions between the 6 and 10 cm levels were reported. Of 272 patients, he reported a 67.7 per cent five year survival rate. Then Waugh¹⁰ in early 1949, in a paper discussing the importance of the level of the lesion in the prognosis for carcinoma of the rectum and low sigmoid, reported the five year survival rates of patients having adenocarcinoma of the rectum and low sigmoid colon treated by combined abdomino-perineal resection. In this report on 262 cases operated

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between 1931 and 1940 inclusive by different surgeons of the Mayo Clinic, the five year survival rate was 52.4 per cent. These lesions were above the 6 cm level, similar to those reported by Dixon. This is most difficult for those surgeons who are strong advocates of the Miles procedure in all cases of rectal carcinoma to appreciate, or for the surgeon who believes the sphincter preserving operation is only indicated in selected cases, because the five year survival rate is better in the group where a sphincter preserving procedure was accomplished. These figures of 67.7 per cent and 52.4 per cent represent the general five year survival rate for patients with and without nodal involvement.

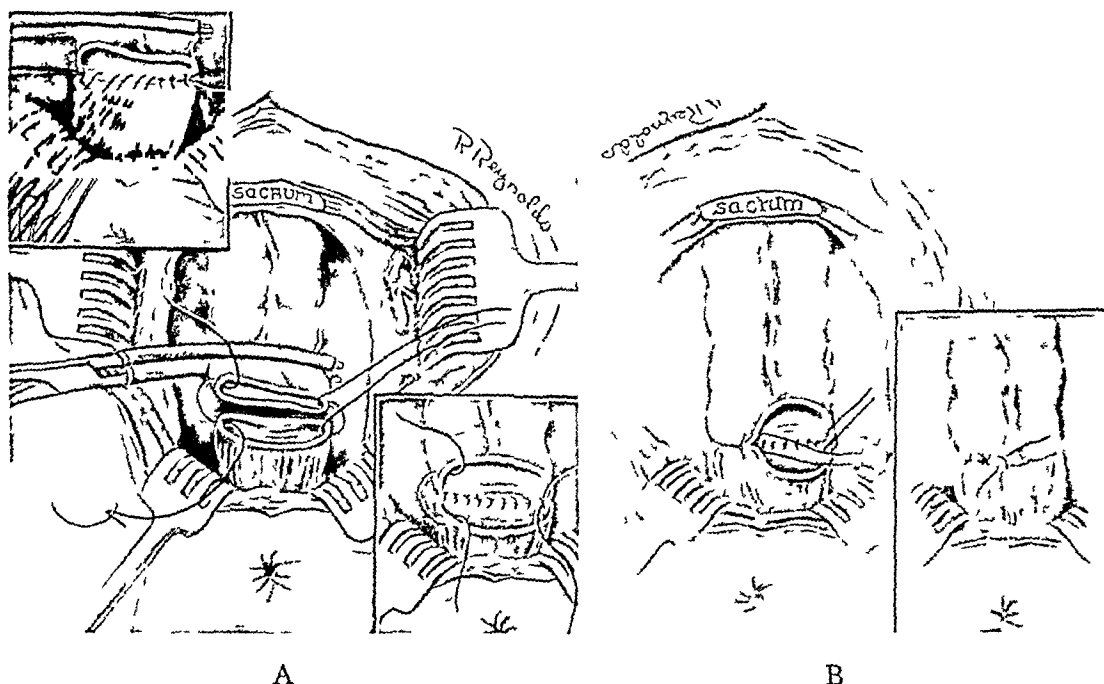


FIG 7—Anterior dissection with posterior resection and anastomosis (A) Traction sutures of catgut are placed at both angles of the anastomosis in such a manner that knots will be on the mucosal wall. A layer of interrupted catgut sutures is inserted on the anterior wall with knots on the mucosal side, inverting the margin of anastomosis. All of these sutures are inserted before any of them are tied. (B) Several similar sutures, with knots on mucosal side, are inserted on the posterior wall. The anastomosis is completed by inserting a layer of figure of eight silk sutures on the posterior wall, lateral walls, and insofar as possible on the anterior wall. The incision is closed and a penrose drain is placed in the hollow of the sacrum and brought out at upper angle of incision.

It is also difficult for us to understand, after a detailed study of the anatomy of the lymphatics and the relation of these lymphatics and the levator ani structures to the rectal wall. However, if our analysis of these reports is correct, and granting unavoidable percentage error either way, the figures are significant and encouraging to those of us who believe in sphincter preserving operations in selected cases. Bacon² with the modified Hochenegg or pull through operation, reports a 52.6 per cent incidence of five year cures. The accepted five year survival rate is probably between 50 and 60 per cent.

Some aspects of the technic are depicted in the accompanying illustrations and in previous reports.^{3,5} Improvements in technic have been made and

complications have gradually decreased. Drainage as a result of leakage at the site of anastomosis has occurred in about 50 per cent of the cases but in only one case did it persist for more than a few weeks. This followed Operation III and the patient died about six months after operation from recurrent carcinoma. We have almost routinely established a cecostomy as a decompressive measure. It is certainly more comfortable for the patient than nasogastric or nasointestinal suction, and is much more efficient when leakage occurs at the suture line. Also, we almost routinely drain the hollow of the sacrum by bringing a small drain out alongside the coccyx or sacrum.

It is our opinion that rectosigmoidectomy with anastomosis is a more satisfactory procedure than the pull-through operation. In our limited experience and observation with the pull-through operation, sphincter control has not been adequate, and the posterior leakage or incontinence is far worse than a colostomy. Also, it is our impression that the technic does not enable one to remove adequately the levator muscle and fascia and the adjacent lymphatics. In fact, we are now of the opinion that our Operation I—rectosigmoidectomy with anastomosis by abdominal dissection, resection and anastomosis—should not be used when the lower margin of the lesion is less than 10 cm from the external anal margin. Of course lower anastomoses are possible and we have done them within 5 cm of the anal margin, but at present we are doubtful of their feasibility. When the lesion is at or below the 10 cm level, or when we believe it is adjacent to the levator and structures, we advocate Operation II—rectosigmoidectomy with anastomosis by abdominal dissection with posterior resection and anal anastomosis—as this procedure enables one to remove the levator and adjacent structures.

SUMMARY

1 Sphincter preserving operations for carcinoma of the rectum merit further study and re-evaluation.

2 The recurrence of carcinoma of the rectum is dependent upon, and the result of, all modes of spread of carcinoma, *i e*, by direct extension, by venous channels, by lymphatic channels, and by transplant. All these factors have been discussed and more emphasis should be placed upon all of them.

3 In a collected series of 607 cases, only 5 patients (8 per cent) had lymph node involvement more than 2 cm below the lower margin of the tumor, yet it is estimated that 200, or approximately 33⅓ per cent, of these patients died from recurrent carcinoma. Some factors other than node involvement below the tumor margin must be considered.

4 After experimental studies by injecting dye into the lymphatics of the perianal, anal and rectal regions, a practical classification of these lymphatics was made. This classification and the relationship between these lymphatics and the levator ani muscles and rectal wall have been discussed.

5 Patients with lesions below the 10 cm level do not have as good a survival rate following radical abdominal-perineal excision as patients with lesions at a higher level. Wider excision of structures laterally to include the

levator ani muscles, fascia and lymphatics is emphasized, when the carcinoma is located in the region of attachment, or adjacent to the levator ani structures

6 Three sphincter preserving operations are presented for malignancy of the rectosigmoid and rectum *Operation I*—abdominal dissection, resection and anastomosis, *Operation II*—abdominal dissection, posterior resection and anastomosis, *Operation III*—posterior dissection, resection and anastomosis

7 *Operation II*—abdominal dissection, posterior resection and anastomosis—is recommended for all lesions below the 10 cm level, as it permits radical excision of the levator structures

8 For lesions involving the perianal skin and not the true anal canal, radium treatment, with or without radiation or dissection of the inguinal lymphatics, would seem to suffice from our studies. Malignant lesions within the anal canal should be extirpated by the radical abdomino-perineal resection

9 The final conclusions on recurrence cannot be reached until a relatively large group of surgeons report on a sufficient number of cases, but the few reports being made on the five year survival rates are encouraging

10 In patients who have had sphincter preserving operations, there is a better opportunity to examine and detect recurrence of cancer in the pelvis. Abdomino-perineal resection can then be done and the patient given another opportunity to survive the disease

11 In our recent series of 51 consecutive cases of rectal carcinoma, there was an operability rate of 86.2 per cent and a resectability rate of 74.5 per cent. In patients with resectable lesions, a sphincter preserving operation was accomplished in 76.3 per cent and the abdomino-perineal resection with sacrifice of the sphincter mechanism was done in 23.6 per cent

12 The operation should be fitted to the location and level of the disease rather than the surgeon fitting the disease to his choice of operation

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DISCUSSION—DR VERNON C DAVID, Chicago There has been an increasing number of suggestions made for local operations of low-lying carcinoma of the rectum and for preserving the sphincters All efforts to improve on the surgical treatment of cancer in the rectum, of course, are highly commendable, providing the patient's chances for long-term survival are not jeopardized

At the present time our own figures show that long-term survival in low-lying cancer of the rectum is greatly lessened by more frequent local recurrences than in the group within the peritoneal cavity This is true in spite of the most radical operations we have been capable of carrying out

What are some of the reasons for this? Below the peritoneal reflection the rectum is enclosed by fascia and muscle attachments which bring the bowel in close continuity to the base of the bladder and soft parts, vagina, prostate, posterior urethra and so on

Widespread resections of these structures are not feasible, and while portions of these structures are not infrequently removed (almost 20 per cent of our own patients had some portion of these organs removed), the tumor very frequently penetrates the bowel wall, and it is obvious that danger of local recurrence exists

In addition, new patterns of lymphatic spread are present, some of which are not removable This is true particularly of the vagina and levator muscles It is undoubtedly true that it is difficult to inject some of the lymphatic pathways traversing the levator muscles, but it has been our experience that they exist I have at present in the hospital a patient whose carcinoma of the rectum had definite lymphatic node involvement in the levator muscles at least three inches away from the tumor

In my judgment this adds up to the necessity of performing the most widespread removal of soft parts possible in lowlying carcinoma of the rectum The technical ability to do an end-to-end anastomosis deep in the pelvis or preservation of the continuity of the bowel, no matter how desirable, should always be considered secondary to permanency of cure of the patient

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It also seems to me that advocacy of limited operation for cancer of the rectum should be accompanied, in the last analysis, by a declaration of the resectability rate, which is a very important thing, the mortality rate, the five-year-plus cure of the patient, the estimation of the malignancy of the tumor based on Broder's, Dukes' and our own criterion of lymph node involvement, and the definite statement as to whether the patients were a selected group or comprised unselected material

It is only by some such standardization that we believe the truth which we all so earnestly seek shall be known

DR THOMAS E JONES, Cleveland, Ohio Dr Best's experiments were on animals Mine have been on humans I have a report to make today on ten-year survival rates which might be of interest

(Slide) In 1938 and 1939 we did 102 abdominoperineal resections for carcinoma of the rectum Each specimen was subjected to minute pathological examination after the method of Drs Dukes, Collier, David and Gilchrist with which you are all familiar

We have a complete follow-up on 96 cases as demonstrated in these slides Since they were completed we have a follow-up on three more cases so we know exactly what has happened to 99 per cent of this series The figures referred to later include everybody as having died from cancer Four cases with liver involvement at the time of operation were not excluded

(Slide) This is an important slide For purposes of information we arbitrarily divided the group into cases that had 0 to 5 nodes involved and those who had more than five nodes involved and you can see the difference in the survival rate There were 78 cases with less than five nodes involved At the end of five years, 44 out of 73 were alive—60 per cent At the end of ten years, 14 out of 28, or 50 per cent were alive

(Slide) However, in the cases that had more than five nodes involved (24 cases in this group), you will notice a marked difference In 22 cases only five are alive, or 22 per cent Twenty per cent were alive at the end of nine years and 11 per cent at the end of ten years You will see then a tremendous drop from 60 per cent in the first group to 20 per cent in the second group This is, of course, a plea for earlier diagnosis

Now, let us look at a group in which there was venous involvement In this group venous involvement was demonstrated in 10 per cent of the cases However, if more meticulous examination were made with special stains, I feel that probably 20 or 25 per cent would show venous involvement

(Slide) In the 92 cases without venous involvement, the percentage of survival parallels the group with less than five nodes involved—viz, 60 per cent 5-year and 50 per cent 10-year survivals

(Slide) However, with venous invasion you will again notice a distinct drop There were ten cases in this group Three were alive at the end of five years, or 30 per cent, as against 60 per cent in cases without venous involvement The 30 per cent survival rate in this group remained the same for the ten-year period

(Slide) This final slide shows the over-all statistics

Number of Cases 102			
	Followed	Alive	Per Cent Surviving
5 years	97	51	52.5
8 years	94	46	48.9
9 years	73	36	49.3
10 years	32	14	43.7

I show these slides merely to point out that if these are the best results we can obtain with the most extensive operation, I do not see much use in fiddling around with smaller or so-called sphincter-saving procedures

DR CLAUDE F DIXON, Rochester, Minn My remarks will be limited to the treatment of cancerous lesions which occur in the lower half of the rectum

First, I think that we are in agreement that the results which follow the surgical removal of cancerous lesions affecting the colon and the rectum are less satisfactory when the lesions occur in the most distal segments of the large intestine

It is understandable why some of us have been eager to attempt to maintain the sphincter and normal bowel control on removal of the lower part of the rectum by means of the method of Hochenegg A small pedunculated or sessile carcinoma of the lower portion of the rectum doubtless may occasionally be cured by a surgical procedure other than radical resection with establishment of some type of abnormal or artificial anus The fact remains, however, that the majority of cancerous lesions of the lower half of the rectum are not small lesions and they spread centrifugally as well as proximally by means of the lymph and blood stream and by direct extension

For several years I have been of the opinion that the surgical removal of cancerous lesions, situated low in the rectum, requires an even more radical operation than the Miles procedure, for involved lymph nodes may be found in the pelvic fascia and levator ani muscles at a distance of 2 to 3 inches (5 to 7.5 cm) from the lesion in the bowel For this reason, in a large series of patients suffering from cancer in the lower part of the rectum, I have carried out a two-stage combined abdominoperineal resection The abdomen is explored through a low left rectus incision If the abdomen is found to be free of metastatic processes, the bowel is divided in the distal portion of the descending colon and the proximal end is brought out through the abdominal wall in the left lower quadrant by means of a stab wound, muscle-splitting type of incision

Next the posterior parietal peritoneum is opened, the superior hemorrhoidal vessels are ligated and severed, and then the first portion of the sigmoid colon with its mesentery is removed The bowel is now divided in the region of the midsigmoid, the proximal end of the remaining segment is inverted and allowed to remain free in the upper portion of the pelvis, the small defect or the incised posterior parietal peritoneum is repaired, and the abdomen is closed in the usual manner Later (in ten to 12 days) a radical perineal operation is carried out, at which time portions of the gluteal muscles, the levator muscles and pelvic fascia are removed The peritoneum is opened and the rectum and remaining segment of sigmoid and mesosigmoid are removed Then the peritoneum is closed, and the wound is packed with four yards (about 366 cm) of gauze four inches wide (10 cm) which is removed on the fourth postoperative day This procedure is carried out with the patient in the reverse Trendelenburg position and is, I believe, radical in the region of the growth which to me seems to be indicated

My personal experience with the pull-through operation is that it frequently fails because of local recurrence of the lesion or because the mechanism of the involuntary sphincter (internal sphincter) is destroyed Finally, I think it well to keep in mind that the meticulous work of David and Gilchrist, and of Collier and his associates has demonstrated that, in cases of rectal cancer, involved lymph nodes may easily be overlooked Therefore, as a rule, I think that some type of radical operation is the operation of choice in the surgical management of cancer of the lower portion of the rectum

DR R KENNEDY GILCHRIST, Evanston, Ill Gentlemen, I think one of the troubles here is what the different surgeons mean by a "radical" operation, secondly, where is this cancer that they are discussing?

It is very interesting to go through the pathological material removed by men who are trained under pretty much the same auspices in one single institution, and to see the different amount of tissue and the lymph drainage removed by various surgeons,

and then go back and look at your own specimens, you will be surprised I find, too, that I have been much less radical some times than other times

What is a radical operation for cancer? The word is used by almost every surgeon who operates for cancer To my mind it means the removal of the tumor, the surrounding soft parts as widely as they can be removed, and all of the primary and all of the first alternate group of lymph nodes that drain the area, if it is possible to do so, and still have a living patient who can carry on his normal life

The studies on lymphatic drainage shown here confirm what has been shown before Squamous cell carcinomas that arise in the skin and involve the mucosa of the bowel, or come up behind the mucosa, we have demonstrated to have lymph node metastases upward along the superior hemorrhoidal drainage as well as to the inguinal nodes Of course that is just what one would expect from an anatomical study of the lymphatics

By the same token, those adenocarcinomas which arise in the mucosa and have extended downward to involve the skin—we have seen some where there has been lymphatic involvement of the inguinal nodes as well as to nodes along the superior hemorrhoidal vessels Any local operation for cancer at this level must be viewed with a good deal of reserve Certainly it cannot be called radical surgery if you do not take out the regional lymph nodes

(Slide) This is not new This man had a very lowlying carcinoma

(Slide) Rouviere showed this same thing, that there are lymph channels very low in the rectum which may go directly to the nodes at the promontory of the sacrum This patient had a lesion just above the mucocutaneous line, and yet there are involved lymph nodes at or above the promontory of the sacrum, and of course no posterior resection is going to remove these

To my mind the superior hemorrhoidal arteries should be removed at least an inch and a half, and preferably two inches above the promontory of the sacrum if you have any hope of removing the primary set of filters to the lower bowel The lateral spread has been well discussed

I would urge upon you two other things Let's have a common landmark that we can identify I know of a patient in Chicago who had a proctoscopic examination by a medical man He found a tumor about nine or ten centimeters above the mucocutaneous line The patient did not want a colostomy, she went elsewhere and had a transverse colon resection for a carcinoma which had intussuscepted all the way down If we are to use centimeters on the proctoscope as a landmark, this tumor would be classified as one at nine centimeters

The landmark you can see any time on the specimen or in the belly, and that needs no ifs, ands or maybes, is the deepest part of the pelvic peritoneum Of course, as Dr David has pointed out, this region has an anatomical importance as far as lymphatic drainage and fixation to the contiguous structures which may set up new lymphatic drainage patterns The anterior peritoneal reflection is the landmark that I would urge, rather than centimeters, because it is reproducible and needs no further identification For many years we have often re-established continuity where lesions were ten or 12 cm on the proctoscope by obstruction resection I was brought up on that

If you remove the bowel and its mesentery an inch and a half or two inches below the tumor, and if the tumor is covered completely by peritoneum on the anterior surface and if there is no marked enlargement of the lymph nodes or fixation to other structures, there is no reason why you should not attempt to re-establish continuity, but if any of these unfavorable features are present, then you must do the most radical thing, namely, an abdominoperineal resection

DR R. RUSSFELT BIST, Omaha, Neb I would like to thank the discussers for their interesting and informative remarks

First, I would like to make a few remarks about the pull-through operation The operations I have seen done, and also those depicted in the literature, do not seem

radical enough in the region of the levator ani muscle. In this whole picture we have three avenues of spread. I plead that we stay just as high above the lesion as possible, because that is the most direct method of spread. From our studies, I also plead for more and wider dissection of tissues in the region of the levator ani muscles. When it comes to considering the area below the lesion, our investigations lead us to believe that the sphincter mechanism can be saved more frequently than it has been in the past.

Theory and emotion must be replaced by experience in sphincter preserving operations and a final tabulation of the end results. Personally, I do not believe that sufficient experience has been had by a sufficient number of surgeons in a sufficient number of cases over a long enough period of time to unequivocally make a statement. In this presentation, I have merely attempted to evaluate the sphincter preserving procedures based upon existing pathologic-anatomical knowledge, some experimental studies and a limited experience.

In the pull-through procedure, I do not believe we have good control in many cases and if we do not have good control, whether by anastomotic procedure or pull-through, I believe it is better to have an abdominal anus. A well and tried fecal discharging stoma on the abdominal wall is far better than a hidden irritating fistulous opening in the perineum.

Next, a few remarks on technic should be mentioned as related to this group of patients.

(Slide) In our cases we have always established a cecostomy and have always drained the pre-sacral space by a small incision along the coccyx in all operations where the anastomosis is below the peritoneal reflection. In other words, in Operations I, II and III these two technical maneuvers seem indicated by us to lessen morbidity and mortality.

(Slide) In our posterior approach in Operation II, we go more widely than depicted in these drawings. From our experimental studies, we are now more conscious about wider excision in the region of the levator ani muscle in the abdomino-perineal operation and in the sphincter preserving procedures.

(Slide) This shows the completion of the anastomosis and placing of a drain in the hollow of the sacrum, because in about 50 per cent of our cases (I am reluctant to say it), we have had some fecal drainage although in only one case has it been prolonged over any number of weeks.

EXTENSION OF CARCINOMA OF THE STOMACH INTO THE DUODENUM AND ESOPHAGUS*

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UNIVERSITY OF CINCINNATI AND THE CINCINNATI GENERAL HOSPITAL

THERE IS CONSIDERABLE REASON to believe that many surgeons today are performing inadequate removal of cancer of the stomach, because of deficient knowledge as to the nature of its spread. The poor results which are generally recognized to exist so far as complete cure of this disease is concerned are usually ascribed to the fact that in the vast majority of cases the cancer is far advanced by the time operation is performed and dissemination to distant areas has already occurred. On the other hand in some of the large bulky lesions the tumor remains localized in the stomach for a considerable time without metastases. While many efforts to improve the situation as regards earlier diagnosis are being made, it seems unlikely that any major improvement will occur in the near future. For that reason it seems desirable that surgeons should review their present methods, and in the light of present knowledge of the spread of the disease, see if changes in them can lead to increase in the percentage of cures.

For the past 18 months we have been engaged in a study of the extension of cancer of the stomach into the wall of the organ itself and also into the duodenum distally and the esophagus proximally, using large microscopic sections. This investigation has been supported in large part by a research grant from the National Cancer Institute, U S Public Health Service. Previous studies of such extension have been made, but though a number of reports concerning it have been recorded they have not received wide publicity, and we are convinced that many surgeons who are resecting stomachs for cancer are unaware of the importance of the local extension which frequently occurs.

In 1934, Verbrugghen¹ reported a study of 50 cases of cancer of the stomach with regard to the local extension of cancer in the gastric wall. His material consisted of specimens removed surgically at the Mayo Clinic. He found that the degree of extension varied considerably, depending largely on the degree of differentiation of the tumor microscopically. In many infiltrative types the extension was found to be considerable and unpredictable. On the other hand in those lesions which were well localized grossly, there was found to be microscopic extension as much as 35 mm from the apparent edge of the tumor. Verbrugghen therefore recommended that a margin of at least 4 cm of apparently normal tissue be removed beyond the edge of well circumscribed lesions,

* Supported in large part by a grant from the National Cancer Institute, U S Public Health Service. Read before the American Surgical Association, St Louis, Mo., April 21, 1949.

and stated that even wider margins were desirable in lesions less well defined

In 1936, Castleman,² in a review of 134 surgical and 65 autopsy specimens of the stomach, by careful microscopic study, found infiltration of cancer cells beyond the pylorus into the duodenum in 21 cases, or 10.5 per cent. That such spread could occur was not generally recognized or mentioned in textbooks. As a matter of fact, it has been a popular misconception that cancer of the pyloric end of the stomach remains well confined within the stomach itself and does not spread beyond the pylorus. He reported that the extent of penetration of the duodenum varied from 4 to 23 mm. and he therefore recommended that at least 3 cm. of duodenum be removed in resecting every carcinoma of the pyloric end of the stomach.

In 1941, Coller, Kay, and McIntyre³ published their very important contribution to our knowledge of the lymphatic spread of cancer of the stomach especially in the extramural lymphatic system. In the 53 cases studied by them, principally with regard to the lymphatic spread, they mention that in 14 or 26.4 per cent there was microscopic evidence of extension of the cancer into the duodenum.

Pack and McNeer⁴ in a recent article have pointed out the frequency with which cancer of the cardiac end of the stomach has invaded the wall of the esophagus. This involvement, just as in the duodenum, is likely to be only microscopic, and therefore imperceptible to the surgeon on gross palpation, and may extend for considerable distances. They state that this extension has been observed so frequently, and may extend so far, that their routine procedure is to make a frozen section of the transected esophagus, and anastomosis is not done until such examination has been reported negative for cancer.

The material for our study has been obtained principally from the operating rooms of the Cincinnati General Hospital and the Christian R. Holmes Hospital. Both of these hospitals are under the professional direction of the College of Medicine of the University of Cincinnati, and the operations were performed by members of the faculty of the Medical College and the resident house staff. In addition, a number of specimens were obtained from four private hospitals in Cincinnati, so that many surgeons participated in furnishing the material, and examination gives a picture of how resections of the stomach are performed in the city as a whole. A number of autopsy specimens have been studied during the same period and by the same method. These are not being reviewed at this time, as they may be considered by some as representing more advanced stages of the disease than those which were considered operable and removed surgically.

The steps involved in the study of our cases included the following: The pathologist received the specimen as promptly as possible after its removal. Usually he was in the operating room to get it immediately. The specimen was opened and after gross examination and description, was photographed in color and black and white, pinned out on a cardboard or thin board to minimize shrinkage, and fixed in formalin. After fixation the artist made a sketch of the lesion, and the portion taken for microscopic study was indicated on this sketch.

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by dotted lines. Large blocks were taken through the entire lesion and through the adjoining stomach and duodenum or esophagus to the edge of the specimen. In a number of instances one block sufficed to reach from one end of the entire specimen to the other, sometimes two or more were necessary. The chief limitation to the size of the block was the size of the slide and cover slip, the dimensions of which are approximately 3 by 5 inches. The tissue was imbedded in paraffin, cut on a special microtome, usually at 10 micra thickness, and stained with hematoxylin and eosin. The thinness and general excellence of the sections was such that careful microscopic study was possible. In general the blocks were 5 to 10 mm in thickness, and though serial sections were not made, a number of sections were prepared from several levels in each block so as to give a better picture of the extent of invasion.

The total number of operative specimens examined to date is 47 divided as follows

TABLE I

Partial gastrectomy including duodenum	34
Partial gastrectomy, including esophagus	6
Partial gastrectomy, including no duodenum or esophagus	5
Total gastrectomy	2
	—
Total	47

In most of the tumors of the distal half of the stomach, the resection was carried beyond the pylorus. In a few, although the gross description and photograph seemed to indicate that some duodenum had been resected, no duodenal mucosa could be recognized microscopically. Of the total of 36 cases showing duodenal mucosa microscopically, nine or 25 per cent showed invasion of the duodenum by carcinoma. In six of the 36 cases the lesion was in the body of the stomach and grossly more than 5 cm from the pylorus. If these are excluded and only the 30 cases considered in which the lesion was located in the antrum and within 5 cm of the pylorus, the percentage of cases in which duodenal invasion was found is 30 per cent, or 9 cases out of 30. The length of extension could not be measured too accurately, but varied considerably, being only 3 mm in two cases, from 7 to 15 mm in four cases, 20 mm in two cases and 60 mm in one case. These measurements were made directly on the large sections, and do not allow for any shrinkage which had occurred (See Table II). The invasion into the duodenum seemed principally to be by direct infiltration of the muscle or extension in the subserosal lymphatics. In only three cases was it in the submucosa, one of the chief sites for extension in the stomach and esophagus. In a number of cases an isolated lymph node adjacent to the duodenum beyond the pylorus displayed metastasis without any actual cancer being found in the duodenal wall itself. Such instances have not been listed as showing extension into the duodenum, though it is obvious that removal of a node in this location *en bloc* with the rest of the specimen would require resection of the duodenum. In practically all cases there was no gross

evidence of invasion of the duodenum, and it was recognized only microscopically

The greatest extension encountered was 60 mm as measured on the resected specimen. In this case, however, carcinomatous infiltration was

TABLE II—*Degree and Location of Extension into Duodenum*

Case No	Extent	Location
11	3 mm	Mucosa
12	60 mm	Muscle and subserosa
21	15 mm	Muscle
23	7 mm	Muscle
59	20 mm	Lymph node and muscle
65	12 mm	Subserosa
78	10 mm	Submucosa
79	3 mm	Mucosa and muscle
80	20 mm	Muscle

present at the line of division of the duodenum so that it obviously extended farther than that. This patient was operated upon by one of us (MMZ), and at the operating table peculiar radiating lines were seen extending in the subserosa of the duodenum well into the second portion. It was suspected that this might represent carcinomatous extension, but was unlike any seen previously and therefore not regarded as characteristic. The patient had a deep ulcer, but there was free hydrochloric acid in the gastric secretion, and there was some question whether the patient had cancer or a benign ulcer. Radiating lines similar to those seen in the serosa of the duodenum were found extending over the pancreas and the retroperitoneal tissues from near the base of the ulcer. No enlarged lymph nodes nor metastases in the liver could be made out. During resection more duodenum was removed than usual in order to get a good specimen of the unusual appearing tissue, though the total visible extent of what later proved to be cancer could only have been removed by total pancreatectomy and duodenectomy. The microscopic picture shows extensive cancerous infiltration in the subserosa and muscularis up to the line of resection. As can be seen in Fig 1, the section resembles a typical benign gastric ulcer, which is just the way it appeared at the operating table. There is, however, both scirrhous and mucoid carcinoma present in the base and wall of the ulcer with wide spread extensions both in the muscle and in the subserosal lymphatics. Most of these groups of cancer cells are too small to be seen in Fig 1. On low power examination, Fig 2, they can be seen to extend, as has already been noted, to the line of transection of the duodenum, certainly several inches from the distal edge of the ulcer. Proximally, they extend in the subserosa to arrow No 3, Fig 1, 40 mm from the proximal edge of the ulcer. The patient developed jaundice about four months after operation. Shortly thereafter the liver enlarged rapidly and death occurred within six months.

There were six cases of cancer of the cardiac end of the stomach, all removed with some attached esophagus. All but one of these showed microscopic invasion of the esophagus, although this was evident grossly in only two cases. Microscopic extension into the esophagus occurred principally in

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the submucosa with additional extension in the longitudinal and circular muscle in some cases. It consisted usually of small isolated clumps of cancer cells, apparently lying within lymphatic channels. It is our impression that the extension developed first in the submucosal lymphatics and as it progressed, extended outwards into the lymphatics in the muscle layers. The longest extension measured was approximately 25 mm, but at that point the esophagus had been resected, and it is impossible to say how much farther extension had



FIG 1—Section of cancer of stomach resembling benign ulcer (1) Junction of gastric and duodenal mucosa (2) Cancer cells in serosa and muscularis to edge of transection 60 mm from pylorus (3) Cancer cells in serosa 40 mm from the proximal edge of the ulcer

occurred. This is illustrated in Figs 3, 4, and 5. The tumor itself, as can be seen in Fig 3, is a small, sessile adenocarcinoma with superficial ulceration. It measured only about 35 mm in diameter and seemed to be rather sharply localized. The exact junction of the gastric and esophageal mucosa cannot be recognized but is presumably at about the level of arrow No 1 in Fig 3. Distally in the stomach small clumps of cancer cells can be seen in the submucosa as far as arrow No 2, Fig 3, approximately 45 mm from the edge of the tumor. These are shown in a low power photomicrograph in Fig 4. In the muscularis they do not extend quite so far, about 35 mm from the edge of the tumor. Proximally, the tumor cells extend both in the submucosa and in the muscularis to the line of transection of the esophagus,



FIG 2—Low power photomicrograph ($\times 20$ before reduction) of area 2 in Fig 1. Arrows point to cancer invading muscularis and serosa to edge of transection

about 25 to 28 mm from the upper end of the tumor. This part of the section is shown in low power magnification in Fig 5.

The extensions in the wall of the stomach varied within wide limits and were unpredictable. In many of our cases the microscopic spread was not

FIG 3

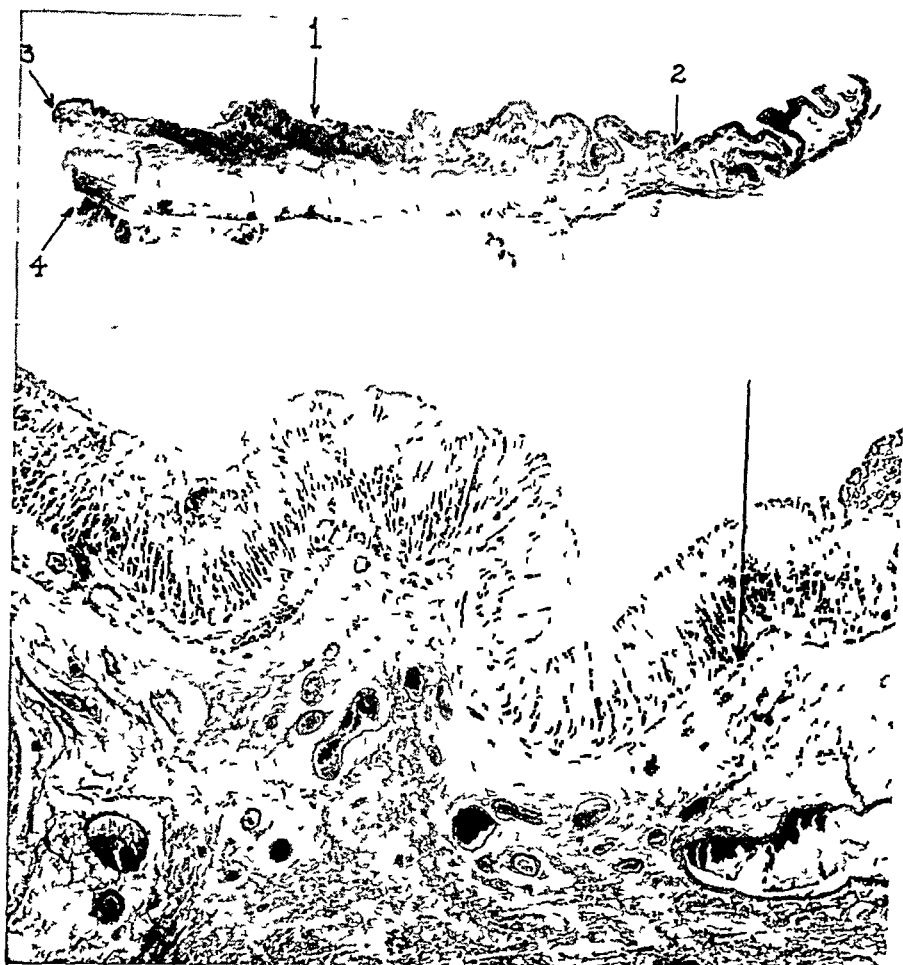


FIG 4

FIG 3—Section of cancer of cardiac end of stomach including stomach and esophagus. (1) Approximate position of gastro-esophageal junction. (2) Limit of extension of cancer into stomach in submucosa. (3) and (4) Extension of cancer in submucosa and muscularis to point of transection of esophagus.

FIG 4—Low power photomicrograph ($\times 20$ before reduction) of area 2 in Fig 3. Arrow points to limit of cancer extension in submucosa. Tiny clumps of cancer cells can be seen in the submucosa almost continuously from here to the tumor.

significantly beyond the obvious gross limits of the tumor. In most instances it varied from 5 to 10 mm, but in some cases was as much as 15 to 25 mm. We were unable to find any correlation between the microscopic nature of the tumor and the extent of microscopic spread. Neither was there any way in which we could predict from the gross appearance how far extension would occur. In

general it seemed that the ulcerative lesions which grossly resembled benign ulcer were likely to spread most widely beyond the gross limits. In the stomach as in the esophagus, the principal site for extension seemed to be in the submucosal lymphatics. In scirrhous carcinomas, however, direct extension in the muscle was likely to be present, though this was usually evident grossly or at least suspected because of thickening and induration. The submucosal extensions as a rule were not associated with thickening of the wall or palpatory evidence, and consisted of inconspicuous clumps of cancer cells as seen in Fig 4.

It was noted in Table I that in five cases no duodenum or esophagus was present in the sections. These represented either small lesions located in the fundus, or else cases in which the distal end was transected so close to the pylorus that all of the duodenum removed was crushed by the distal clamp. One of these was a very small, and presumably early, lesion which is of considerable interest. In this patient, gastro-intestinal roentgenological study for discomfort due presumably to spastic colitis demonstrated a polyp in the fundus of the stomach. Gastroscopic examination confirmed the presence of the polyp, but malignancy could neither be diagnosed nor excluded. At operation within ten days of the discovery of the lesion we also were in doubt as to the nature of the polyp, which was soft and about 2 cm in diameter. A radical resection nevertheless was performed and the microscopic section showed a benign polyp about 1½ by 2 cm on a short pedicle. Just at the base of the polyp was a small carcinoma about 12 by 5 mm in diameter. Even this small lesion showed one tiny nest of cancer cells in the muscularis about 3 mm from the edge of the tumor. No involvement of any lymph nodes was found. Only a small segment of duodenum was removed at operation since the tumor was at least 4 inches from the pylorus. No duodenal mucosa was seen in the section which undoubtedly was due to the fact that it was crushed in the distal clamp.

The two total gastrectomies in this series were for extensive lesions, one for a large carcinoma of the lesser curvature, and the other for a case in which there were multiple malignant polyps. In neither instance could the



FIG 5—Low power photomicrograph (x 12 before reduction) of areas 3, 4 in Fig 3. Arrows point to tiny clumps of cancer cells in submucosa and muscularis.

surgeon be sure about the exact extent of the lesion, and therefore performed total gastrectomy in order to keep well beyond any extensions of the tumor. In neither case was there invasion of either duodenum or esophagus, grossly or microscopically.

From an examination of the microscopic sections, a significant number of the cases showed that the surgeon had either cut through cancer at one or the other end of the specimen or had resected so close to tumor as to make one believe that there was insufficient margin of normal tissue. In actual figures this is shown as follows: Total cases 47. Cancer in transection line of stomach seven, of duodenum one, of esophagus one. Thus there were nine instances in the 47 cases in which the surgeon cut across carcinomatous tissue in the resection, approximately 19 per cent of the cases. It is interesting to note that

FIG 6



FIG 7

FIG 6—Section of ulcerative cancer of prepyloric area (1) Junction of gastric and duodenal mucosa (2) Extension of cancer into muscularis of duodenum (3) Proximal extent of cancer in submucosa of stomach

FIG 7—Section of ulcerative cancer of prepyloric area (1) Junction of gastric and esophageal mucosa (2) Distal extent of cancer microscopically (3) Proximal extension of cancer in muscularis and serosa to line of transection

in 1941 Coller and his associates in the article previously cited made somewhat similar observations. It must be emphasized that just as in Coller's series a fair number of these patients presented far advanced lesions, and many of the resections were palliative procedures and were not considered by the surgeon as being curative. Several such cases were done by one of us (MMZ), and resection was performed, even though it was obvious that not all of the carcinoma could be removed, in an effort to relieve nausea, anorexia, pain, obstruction, bleeding or vomiting, and with the expectation that death would

occur from metastases or general debility before local recurrence led to the return of symptoms referable to the stomach itself

Consideration of the data presented here, together with that presented by others, leads us to believe that many surgeons not only are not being sufficiently radical as regards removal of the extramural lymphatics, but that also they do not remove sufficient amounts of stomach, of duodenum, or of esophagus. In all carcinomas of the distal half of the stomach, in addition to removal of the great omentum, and as much of the gastro-hepatic ligament as is possible, the first portion of the duodenum should also be removed. Just how far the resection should be carried proximally in the stomach cannot be stated in centimeters or inches, but it would seem wise to suggest that the surgeon decide what he regards as a safe margin proximal to the tumor and then actually resect an inch or two more. Naturally the question arises as to the desirability of routine total gastrectomy in the treatment of gastric cancer. This has already been suggested by Longmire.⁵ Our own experience with total gastrectomy leads us to believe that marked feeding difficulties occur in a fairly large proportion of patients, though others seem to have little or no difficulty in eating after apparently identical procedures. On account of these feeding difficulties we are not willing as yet to recommend routine total gastrectomy.

For cancers of the cardiac end of the stomach we believe that resection of some esophagus along with the cardiac end of the stomach is necessary. Just how much esophagus should be removed is not certain, but 1 to 1½ inches may prove to be too little. The plan recommended by Pack seems to be worth consideration by all of us, i.e., frozen section of the cut end of the esophagus before anastomosis is done.

We have been more and more impressed by the value of a combined abdomino-thoracic incision for the removal of all cancers of the stomach, whether they be in the distal or proximal half of the organ, and whether a total gastrectomy is to be done. For this purpose we have been using the incision described by Carter⁶ for splenectomy. This incision gives adequate exposure of the duodenum so that its resection can be carried out readily. It gives admirable exposure of the gastro-hepatic ligament and permits easy access for removal of gland-bearing tissue along the lesser curvature of the stomach, and with slight modification allows exposure and removal of a considerable segment of the lower esophagus. We are now using it almost routinely in all cases of cancer of the stomach.

SUMMARY AND CONCLUSIONS

Forty-seven cases of cancer of the stomach have been studied with reference to extension of the tumor into the wall of the stomach and into the duodenum and esophagus.

In 30 cases in which the tumor lay grossly within 5 cm. of the pylorus, nine or 30 per cent showed carcinomatous invasion of the duodenum. The extent of this invasion varied from a few millimeters to several centimeters. In

practically every instance the invasion was only evident microscopically and was not recognized grossly

In six cases of cancer of the cardiac end of the stomach, five showed invasion of the esophagus, though this was apparent grossly in only two of them. The greatest length of microscopic invasion beyond the apparent edge of the tumor was 25 mm.

In the wall of the stomach, microscopic invasion varied greatly with regard to its extent.

No correlation could be recognized between the gross or microscopic appearance of the tumor and the likelihood of invasion.

In view of these findings it seems advisable to reaffirm the need for wide local excision in resecting cancer of the stomach. In order to accomplish this easily, a combined abdomino-thoracic incision is recommended.

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DISCUSSION—DR. ALEXANDER BRUNSCHWIG, New York City. I simply want to use Dr. Zinninger's excellent presentation to present a few photographs that might be of interest to the Association in connection with the subject of gastric cancer. These are photographs that relate to the initial operation that Billroth performed in 1881.

(Slide) This is the specimen of the first gastrectomy as it is preserved today in Vienna. You will note that Billroth did remove quite a generous part of the first segment of duodenum. The date of the operation was January 19, 1881. The photograph was sent to me by Professor Denk of Vienna, who was elected to honorary membership in this society last year.

(Slide) This is the front sheet of the original history of this epoch-making case. There is no signature to this discussion of the patient's symptoms. The physical findings begin about here. We don't know who wrote the history, although presumably it was one of Billroth's assistants.

(Slide) This is a postoperative note made the day after operation, and again it is unsigned. This is a freehand pencil sketch which is remarkably well preserved, with the pylorus indicated here, the tumor here, and the cuff of the duodenum here.

It is interesting to recall that Billroth was rather fearful of criticism, and scheduled this operation late one afternoon under the seats of his amphitheater, and only two or three of his assistants knew that he was going to do it. They were the only audience present.

(Slide) This is the final note: "Died of metastases after pylorotomy for cancer," and it is unsigned. The patient had lived four months.

THE END RESULTS OF COMPLETE VERSUS INTRACAPSULAR REMOVAL OF ACOUSTIC TUMORS*

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THE SO-CALLED ACOUSTIC TUMORS are the common type of intracranial new growths situated in the cerebellopontile angle. Although they are benign, encapsulated, non-invasive lesions, their removal in the early days of neurosurgery was attended with such a high mortality (75 to 85 per cent) as to be prohibitive, and even then it is doubtful whether complete removals with useful survival of the patients were ever accomplished.

In 1917, therefore, Harvey Cushing² introduced the method of what he termed the "intracapsular extirpation" of these tumors. This meant that after incising the capsule, the contents of the growth within were more or less completely taken out with a blunt curet combined with suction. In this way it was inevitable that some portions of the tumor would remain inside the capsule, as the latter was left *in situ*, and recurrence took place at varying intervals, many within two to five years following the operation, although a fair number of patients lived for much longer periods. However, the intracapsular operation constituted a great step forward, since, for the first time, it offered patients with acoustic tumors a good chance at least of coming through the operative procedure. The immediate mortality was reduced, at least in Cushing's hands, from prohibitive figures down to 20 per cent at first, and later to less than 10 per cent.

On the other hand, it became obvious that the intracapsular removal was far from ideal, both because of almost certain recurrence and because the five-year mortality after this procedure was exceedingly high—56 per cent in Cushing's series, from figures given by Eisenhardt⁷ in 1935. For this reason Dandy³ made a preliminary report in 1922 of an operation for the complete removal of acoustic tumors, followed in 1925⁴ by recording five such complete extirpations without mortality. In 1934⁵ he introduced an important technical advance in the unilateral approach through a relatively small bony opening instead of the wide bilateral exposure used hitherto.

Since these early articles there have been surprisingly few reports by neurosurgeons concerning the end results of operations for acoustic tumors by either of the methods mentioned. In 1934 Olivecrona¹⁰ reported 31 cases in which complete extirpation had been performed with a 19.4 per cent mortality. He stated that the end results and useful survival in this group were far better than in his previous series of intracapsular extirpations.

* Read before the American Surgical Association, St. Louis, Missouri, April 21, 1949.

In 1939 the present authors reported⁸ a series of 35 patients with acoustic tumors on whom they had operated during the previous seven years. Seven of those patients had intracapsular removals, and although the operative mortality was not great, all but one of these patients died subsequently. Nine other patients had one or more previous attempts at removal of their tumors elsewhere, and although we were eventually able to extirpate their growths completely they need not be considered in the present connection, since the difficulties and hazards in this group are exceedingly great. The remaining 19 patients had not been operated on previously and a complete removal of their tumors was accomplished. The operative mortality in this latter group was 10.5 per cent, and it was stated that, aside from the two postoperative deaths and four others who showed considerable disability, the remainder (68 per cent) "were able to get about perfectly well by themselves and, for the most part, to resume their former occupations."

In 1942 Nielsen⁹ made a careful study of Olivecrona's large series of 130 acoustic tumor patients operated on between the years 1930 and 1939. Twenty-eight of these patients had intracapsular extirpations of their tumors and Nielsen also gave mortality figures for 34 patients with this type of operation performed previously by Olivecrona, making a total of 62 intracapsular removals. There were likewise 75 patients who had had their tumors completely taken out. Without going into the details of Nielsen's statistics it was pointed out that the immediate operative mortality from intracapsular removal was between 27 and 28 per cent and that within five years the death of 16 more patients had occurred, making the total five year mortality for this group roughly 56 per cent. On the other hand, the operative mortality in the completely removed group was 18.7 per cent, and although four of these patients died subsequently, in only one was there the possibility that death was due to tumor recurrence.

In regard to useful survival, that is, either full or somewhat diminished earning capacity, Nielsen stated that 75 per cent of the patients having intracapsular extirpations came into this category. This figure refers obviously only to those patients who survived the operation and the subsequent five-year interval, since only 27 patients, or roughly 44 per cent of the original 62 in this group, survived. As will be shown later, we feel that the only real way of determining correct end results is to base the percentage of useful survival on the total number of patients operated upon. If such a comparison is made, the 75 per cent, or 21 of the 27 survivors, would represent 33.8 per cent of the total 62 patients with intracapsular removals who were leading useful lives.

In the group of complete extirpations Nielsen has again followed the same method of basing the percentage of patients living useful lives on the number surviving the operation and the five-year interval. His figure for this group by this method would be 80.4 per cent, but if one bases the percentage on the total number of patients operated upon, namely 75, it is found that roughly

60 per cent of patients who had complete removal of their tumors were living useful lives at the time they were studied. As can be seen, this figure is nearly twice the percentage of those in the intracapsular group.

In 1943 Dandy* summarized his experiences with 46 patients who had complete removal of their acoustic tumors. There were five deaths in this series, an operative mortality of 10.87 per cent. In connection with the end results he stated that two patients died within one year after leaving the hospital. Concerning useful survival the following statement was made: "So far as I know all the remaining cases are living and well. With few exceptions all are active, and many of them are carrying on their former work in full capacity. Perhaps half a dozen have some degree of uncertainty in walking and have slight ataxia." It is impossible to get any useful numerical percentage as to satisfactory survival in this series, especially since the author includes "several" small tumors which "were encountered when operating for trigeminal neuralgia by the cerebellar route." These would not be considered as the usual type of relatively large tumors which most authors have dealt with in tabulating both their mortality as well as their end results. However, it is safe to assume that Dandy's figures would at least be as good as others who have made similar studies.

Olivecrona's last report in 1948¹¹ is concerned with 250 operations for acoustic tumors. Of these, 185 had complete extirpations, and in 34 the tumors were subtotally removed. In only 26 was the intracapsular method employed. The operative mortality for the entire group was 23.6 per cent, and for the 185 from whom the tumor was completely removed was 24.3 per cent. Ten of these latter died from one to 15 years after leaving the hospital. Because of the impossibility of anything like complete follow-up figures in Olivecrona's series (since many of his patients were in European countries during the war), only rough estimates of the percentage of patients living useful lives can be made. From his figures there were 118 patients having complete tumor removals who had full or somewhat diminished earning capacity. This would be 63.2 per cent of the original 185 patients operated upon by this method, but would represent 84.2 per cent of the 140 who survived the operation and left the hospital. Twenty-six of Olivecrona's patients had the intracapsular operation. Seven of these died postoperatively and seven others subsequently, thus making the eventual mortality 53.8 per cent. Of the remaining twelve nine, or 75 per cent, were in useful life, but based on the original 26 patients this represents only 34.6 per cent.

To summarize the data as given by Olivecrona and by Nielsen from Olivecrona's clinic one may say that the five-year mortality for complete tumor removals (including the operative mortality) would be roughly 25 per cent whereas with the intracapsular operation for a like period the mortality would

* Article was apparently not published. Manuscript was sent to one of us (G. H.) by the author and the figures given are taken from that.

be about 54 per cent. These figures in themselves are significant, but even more so are those for patients living useful lives, since about 60 per cent of those whose tumors were entirely removed came into this category but this was true of only some 34 per cent of the patients who had had intracapsular extirpations. These percentages are based on the number of patients living usefully as compared with the total number of patients operated upon.

Aside from the figures from the intracapsular series of Olivecrona, as given by himself and Nielsen, the only chance of making a comparison of this method with that of complete tumor removal is through a study of Cushing's end results as given by several of his pupils, since in practically all instances Cushing's patients were operated upon by the intracapsular procedure. It is because some doubt has existed as to the relative merits of the intracapsular versus the complete extirpation of these tumors that the present study has been undertaken. There are three principal questions to be answered. First, what is the immediate operative mortality in the two groups, second, what is the mortality after an interval of five years, and third, most important of all, what is the percentage of useful survival of the patients operated upon by the two methods?

In respect to the last question, it was mentioned previously that heretofore the percentage of patients in useful life has been based frequently on the number of those who survived the operation as well as a postoperative period, usually of five years. This method, however, would be quite unfair in the present comparison for the reason, as will be pointed out, that whereas the actual operative mortality may be more or less comparable in the two groups, nevertheless, during the next five years a very large number of patients in the intracapsular group will have died, but only an insignificant number of those whose tumors were totally removed. In other words, let us say that there were 100 patients who had been operated upon by the intracapsular method, and at the end of five years, 50 of these patients had died either postoperatively or within this interval. If 25, or half of these survivors, were living useful lives the percentage of useful life based only on the number of survivors would be 50 per cent, whereas if based on the original 100, it would be 25 per cent.

On the other hand, if 100 patients had had their tumors completely removed and only 20 of these had died postoperatively or during the five-year interval with 40, or half the remainder, in useful life, the incidence of useful living based only on the number of survivors would again be 50 per cent even though there were 40 such patients by this method against 25 by the intracapsular procedure, but based on the original 100 patients the figure would be 40 per cent against 25 per cent by the incomplete method. The real question to be decided is, given a certain number of patients having acoustic tumors, what percentage of that original number may be expected to have survived each type of operation and a five-year interval and to be living useful lives at the end of that time or longer?

RESULTS OF INTRACAPSULAR EXTIRPATION (CUSHING'S SERIES)

The mortality figures here given are taken from Eisenhardt's follow-up report in 1935. The figures for estimated useful survival were derived from reports made on a consecutive three-year series of Cushing's cases by three of his pupils, Van Wagenen,¹² Cairns¹ and Davidoff.⁶

Total patients operated upon (circa 1906-1932)	176	
Total patients living five years or more	77	
Five year mortality (99 cases including postoperative deaths)		56.2 per cent
Useful survival of the total 176 cases	44 or 25	per cent
Useful survival of the 77 five-year survivors	44 or 57.1	per cent

In reviewing the above statistics it must be remembered that many of Cushing's patients were operated upon in the very early days of neurosurgery when the modern adjuncts of electrosurgery and strong suction and antibiotics were not available, but even so his actual operative mortality was exceedingly low, and was reduced in his last 50 cases to 4 per cent. However, the really significant figure is the one which shows that of the original 176 patients only 77 had survived the operation and the subsequent five-year period. So far as the useful survival of the patients in Cushing's series is concerned the figures are admittedly estimated, but these estimates were taken from follow-up studies by his pupils who were at some pains to get an accurate idea of what the patients' disabilities were, if any. To the best of their knowledge about one quarter (25 per cent) of the 40 patients who were followed were living useful lives, but in view of the statistics given by Nielsen and Olivecrona for the intracapsular operation it is altogether probable that this figure should be raised to 33 to 35 per cent, inasmuch as it is undoubtedly true that Cushing's results by this procedure were at least as good if not better than others using this method. Even so, such a percentage falls far short of that for patients who have had their tumors completely removed.

Since no definite estimate of useful survival can be derived from Dandy's publications, and since it was impossible for Olivecrona to follow a considerable number of his patients on account of war conditions, we have attempted to make a comparison of the intracapsular results of Cushing with our own series of total tumor extirpations. We have considered that patients were living useful lives if they had returned to their original occupation or something comparable to it, or, in the case of women, if they had resumed their usual household duties. Certain older patients who came within the retiring age were considered in useful life if they had no great physical disabilities. However, if patients had handicaps such as marked ataxia or weakness, or if they were blind even though their vision had been lost before the operation, they were not put into the useful category.

At this point the question of facial paralysis comes up. With but few exceptions, possibly four in our experience, this is almost inevitable in doing a complete extirpation of acoustic neuromas of any considerable size. In the majority of cases the enlarged internal auditory meatus is filled with tumor

cells, and since these must be curetted out, the facial nerve can only in rare instances be spared. This matter has always been discussed with patients, and in all but one case they have preferred this to a recurrence of their growth. The appearance of the face can be helped considerably by a subsequent anastomosis with either the hypoglossal or the spinal accessory nerve. Only when the facial paralysis prevented them from doing some gainful work has this feature been considered as depriving them of useful life.

Since 1934, when we began to do complete extirpation of acoustic tumors routinely, there have been 83 patients so operated upon. However, as mentioned earlier, nine of these patients had been operated upon elsewhere previously with incomplete tumor removal, and these need not be considered here as they present very great difficulties and hazards. Likewise, two patients having bilateral tumors have been excluded for obvious reasons. There were, therefore, 72 patients who had not been operated upon previously and whose tumors were totally extirpated. There were eight deaths in this group, or an operative mortality of 11.1 per cent. Even though none of these patients have as yet died since leaving the hospital, nevertheless in order to get a strict comparison with Cushing's as well as with other series, we shall consider only the 47 patients operated upon from 1934 through 1944, so that a five-year or more follow-up period may be obtained. These data may be summarized as follows:

Patients previously unoperated upon who have had complete removal of their acoustic tumors

Total patients operated upon (1934-1944)	47
Total patients living five years or more	41
Five-year mortality (same as operative mortality)	6 12.7 per cent
Useful survival of the total 47 cases	31 65.9 per cent
Useful survival of the 41 survivors	31 75.6 per cent

DISCUSSION

From the data which we have been able to gather through a study of our own series and the other available sources there would seem to be little to say in regard to the merits of the two methods here compared since the figures speak for themselves. In other words, if one compares the above figures or the ones given previously for total tumor removals with the results following the intracapsular operation, it will be seen that the five-year mortality (including postoperative deaths) for patients having complete removals runs from about 12 to 25 per cent, while for the intracapsular it is 53 to 56 per cent. Furthermore, of the original number of patients operated upon, some 60 to 65 per cent with complete tumor removal will be in useful life against possibly 35 per cent of those who have had the intracapsular operation.

There can be no question that any operation on an acoustic tumor is a difficult and somewhat hazardous procedure, but with patience and care they can now be removed completely in the vast majority of instances. If this is done, the patient will not only have as good a chance of coming through the operation as by the old intracapsular method, but will also have an infinitely greater chance of living a permanently useful life.

The one most serious drawback to the complete operation is the almost certain facial paralysis, but this can be improved to some extent by an anastomosis, and in our experience every patient with one exception has preferred this disability rather than to be faced with a recurrence of the tumor and a far more serious secondary operation. Olivecrona was able to spare the facial nerve in 15 out of 23 complete extirpations (Nielsen) but this is a much higher percentage than we have found possible. It may be that the sitting position which, of recent years, has been employed for this operation may make it easier to identify and save this important structure.

SUMMARY

A statistical study of the end results following intracapsular and complete removal of acoustic tumors has been made from our own material and from such other sources as are available. The five-year mortality rate for the intracapsular operation is well over 50 per cent whereas for the patients who have had complete tumor removals it is from 12 to 25 per cent. About one-third of the patients with intracapsular removals will be in useful life after five years and about two-thirds of those from whom the tumors have been totally extirpated.

The one great disadvantage of the complete operation is a high incidence of facial paralysis, but practically all patients in our own series have preferred to have this rather than a recurrence of their tumors.

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DISCUSSION —DR FRANCIS C GRANT, Philadelphia, Pa This is an excellent series of cases which Dr Horrax and Dr Poppen have shown us I think it proves beyond very much question that it is better to attempt to remove these tumors completely than to do a subcapsular enucleation The mortality is lower after complete extirpation, and all chances of recurrence are avoided It is true that these tumors grow very slowly and that, therefore, recurrence after subcapsular enucleation may be a matter of years Nevertheless, they always do recur, and complete cure can only be afforded by complete extirpation

There are two points in the surgery of these tumors which must be considered In the first place, every effort must be made to avoid injury to the ninth and tenth nerves, which lie at the lower pole of the tumor If these nerves can be dissected from the capsule of the tumor without damage, complete extirpation can be done with reasonable safety

Secondly, if the brain stem, against which the tumor is almost always plastered, is damaged during the removal of the lesion, again, very serious postoperative complications can result In our experience the most serious postoperative complication is difficulty in swallowing, whether this be due to damage to the vagus or to damage to the brain stem Aspiration pneumonia is a very common sequela, if the swallowing function is reduced

In our series of cases in which complete removal was possible, 32 cases have survived from one to five years, 21, from six to ten years, 6, from eleven to fifteen years, and 6, for over fifteen years Of these 65 patients, 42 are well and working The other 23 had sufficient neurologic deficit to prevent return to their original occupation

I was particularly impressed with Dr Horrax's low mortality If the mortality can be maintained within reasonable limits and the tumor completely removed, there is no doubt that complete extirpation should always be attempted in acoustic tumors

DR HOWARD C NAFFZIGER, San Francisco, Calif I think this paper has given the neurological surgeons a real mark to shoot at I don't know of any carefully reported series with as creditable results

I think the method of analysis that Dr Horrax has used, including operative mortality with five years' useful survival, is really the best sort of criterion Unfortunately, these patients come to the neurological surgeon late, and, as in the illustration by Dr Grant, practically every one that we see comes at a stage in which the tumor is large enough to indent the pons

In the early days the so-called partial removals were not much more than biopsies A partial removal is a rather loose term, because I think many of us have had the experience of a fatality after what we considered a pretty satisfactory partial removal, but have been appalled to find that we have only nibbled out a very small portion Unless the removal is considerable, intracranial pressure persists after operation, and the duration of life is quite short

The future of these people is such that if they are not killed by the tumor they have a considerable expectation of life In going over the last seventy patients of ours I have found that their average age was 41.8 years, which means that many of them are a good deal younger than that

There are two points I would like to make I think the reports in the literature are quite infrequent as to the results of partial and total removal, many of us are not very proud of our results and are inclined not to say too much about them

In this particular series reported, I think you have heard what can be done by two extraordinarily skillful surgeons working together

I am not at all sure in my own mind but that the mortality in the hands of the same surgeons is lower in the case of total removal than in the case of partial removal

REMOVAL OF ACOUSTIC TUMORS

I think the portions left and the sequelae that go with it contribute very largely to the mortality

I believe this was a perfectly splendid paper

DR COBB PILCHER (Nashville, Tenn) As in the case of many other conditions with which we have to deal, such as carcinoma of the stomach, which has been discussed today, it is unwise to make arbitrary rules, and I should like to point out that each case of acoustic tumor should have a decision made on its own merits as to whether or not a complete or an intracapsular removal should be done

In a young person with many years to live certainly the radical removal is well justified. On the other hand, we know that many of these patients are in advanced years at the time they are first seen. The duration of symptoms, for which I have no accurate statistics, but which I would guess to be not less than an average of ten years, indicates the slowness of the growth of the tumor, and suggests the slowness of its recurrence.

Certainly in an elderly person, in whom the risk of damage to the pons, of damage to the blood supply of the brain stem, and risk of facial paralysis and, may I say, also of the fifth nerve destruction which almost always goes with facial paralysis, I would consider that an intracapsular enucleation, by which I mean removal of almost all of the capsule except the small tab in the pars acousticus, is preferable. Let us not make dogmatic rules to cover all cases.

DR GILBERT HORRAN (Boston, Mass) I want to thank these gentlemen for their very kind discussion of this paper.

Dr Naffziger has touched on one point which I should have mentioned in my original giving of the paper, which I did not have time to do, and it is this. I feel greatly indebted to Dr Poppen for his contributions to this paper, because it was he who in the first place urged me to take up the complete enucleation of these tumors, because I had been brought up in the school that thought the intracapsular procedure was the only thing to do. Dr Poppen played the major role very often, and I want to give every credit to him for the results we have had.

In regard to what Dr Pilcher said, he is quite right that one must bear in mind the occasional case of elderly individual who might do well with intracapsular enucleation of the particular kind he mentioned. I would call that, however, a subtotal enucleation, a term such as Dr Olivecrona uses in describing his procedures—the complete, the subtotal and the intracapsular. Even in the best of hands, such as Dr Cushing and Dr Olivecrona, when the operative mortality is well over 50 per cent after five years, I don't see that there is any real question as to which is the best procedure in the vast majority of cases.

ERRATUM

Due to typographical error in Table I of the article titled "Disarticulation of an Innominate Bone for Primary and Metastatic Cancer," on page 96 of the July, 1949, *ANNALS OF SURGERY*, appeared the statement under remarks concerning patient No. 8 "Patient well 14 months after surgery." The length of time should read four months.

STREPTOMYCIN, AUREOMYCIN AND CHLOROMYCETIN EXPERIMENTAL AND CLINICAL COMPARISON*

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Repeated reports have demonstrated the effectiveness of penicillin, streptomycin and the sulfonamides in peritonitis. In addition, preoperative use of these agents has been found to be of value in reducing the incidence of peritonitis in those surgical conditions in which, in the past, it has been relatively high.

Domagk¹ demonstrated the value of sulfonamides in the treatment of peritoneal infections in mice. Bower² and his associates tested the effects of prontosil on the mixed type of peritoneal infection commonly seen in human peritonitis, while Epps³ and his associates compared the merits of sulfanilamide and sulfathiazole. Fauley *et al*⁴ studied the influence of penicillin in experimental peritonitis in dogs. Crile,⁵ in a clinical study, reported the results of treatment with penicillin of peritonitis of appendiceal origin.

Murphy, Ravdin *et al*⁶ have studied the effects of streptomycin in experimental peritonitis in dogs, and, in addition, have shown that it passes into the peritoneal cavity, and frequently reaches a higher concentration than in the blood.

Kay and Lockwood,⁷ in their experimental studies, expressed the thought that peritonitis is a systemic disease. This was based on their gross and microscopic findings at autopsy. They believed that changes in prothrombin time might be of prognostic value.

Pulaski,⁸ in analyzing a series of clinical cases with peritonitis, stated that streptomycin, used alone, is especially effective in spreading and in localized types of peritonitis without a palpable mass. In a personal communication, he states that treatment of early spreading peritonitis with streptomycin and penicillin combined, seems to offer no significant advantage over streptomycin alone. He states, however, that in the management of localizing lesions, combined therapy seems superior.

Several additional antibiotics have been developed since the discovery of penicillin and streptomycin. Bacitracin, aureomycin and chloromycetin are representative of this new group. Bacitracin, which has been found to be effective in staphylococcal and streptococcal infections, was not considered pertinent to this study.

Aureomycin,[†] which is derived from a strain of *Streptomyces aureofaciens*,

* Read before the American Surgical Association, St. Louis, Mo., April 21, 1949.

† This study was aided by a grant from the Lederle Laboratories Division, American Cyanamid Company.

has been shown to possess, in vitro, antibacterial activity against numerous gram-positive and gram-negative bacteria. It appears to be bacteriostatic rather than bactericidal, except in high drug concentrations.

Chloromycetin, which is obtained from filtrates of submerged aerated cultures of a *Streptomyces* sp., has been found to be quite effective against a number of rickettsiae, and several gram-negative bacteria. In vitro, crystalline chloromycetin has been found to be inactive against yeasts and filamentous fungi, inactive against protozoa, moderately active against gram-positive bacteria and *Mycobacterium tuberculosis*, and active against gram-negative bacteria and *Borrelia recurrentis*. Among the gram-negative organisms showing a considerable degree of sensitivity are the Brucellae, members of the salmonella group, and coliform bacteria.

TABLE I—Comparative Sensitivity of Organisms Commonly Found in Peritonitis of Appendiceal Origin

Organism	Penicillin	Streptomycin	Aureomycin	Chloromycetin
<i>Staph. non hemolyticus</i>	Excellent	Moderate	Excellent	Moderate
<i>Str. viridans</i> , alpha	Excellent	Not susceptible	Excellent	
<i>Str. pyogenes</i> beta	Excellent	Moderate	Excellent	
<i>Str. non hemolyticus</i> gamma	Excellent	Moderate	Excellent	Good
<i>Escherichia coli</i>	Not susceptible	Good	Excellent	Moderate
<i>Clostridia</i>	Moderate	Not susceptible		
<i>Proteus</i>	Not susceptible	Moderate	Not susceptible	Excellent
<i>Strept. faecalis</i>	Excellent	Good	Moderate	

Both aureomycin and chloromycetin are well absorbed from the gastrointestinal tract. There are no reports up to the present time of toxic manifestations resulting from the oral administration of chloromycetin. Aureomycin has low toxicity. Nausea and gastro-intestinal irritation, manifested by diarrhea, has been reported.

The influence of both is greatest on the rickettsiae and on the viral agents of the psittacosis-lymphogranuloma group. Their in vitro and in vivo range of activity closely approximates one another. However, unlike chloromycetin, most strains of gram-positive cocci, pneumococci and hemolytic streptococci are actively inhibited by aureomycin.

Woodward,¹⁵ in a presentation at the General Session American College of Physicians, March 30, 1949, reported the therapeutic effects of these two new antibiotics in typhoid fever, undulant fever, tularemia, scrub typhus, murine typhus, rocky mountain spotted fever, as well as epidemic typhus and Q fever. He believes that chloromycetin is clearly the drug of choice in clinical

* The chloromycetin used in this study was supplied by the Research Division, Parke, Davis & Company.

typhoid In tularemia, he states that aureomycin is more effective than streptomycin Chloromycetin has not been tried clinically in tularemia Experimentally, it is less effective than streptomycin

Aureomycin has been found to be of value in lymphogranuloma venereum, psittacosis and primary atypical pneumonia Comparison in these conditions with chloromycetin awaits further clinical trial

In comparing the range of bacterial sensitivity of aureomycin and chloromycetin with streptomycin and penicillin (Table I), it seemed that valuable data might be obtained by studying the individual effectiveness of each of these antibiotics in a mixed type of infection such as occurs in peritonitis Since peritonitis, in dogs, is comparable to human peritonitis, it was decided to study the effects of each of the four enumerated antibiotics in an experimental study on this animal.

Peritonitis was produced by two methods in this investigation One employed the technic introduced by Bower and co-workers, and as modified by Fauley and his associates, the second, which basically represents a second study, employed the technic suggested by Rothenberg, Silvani and McCorkle¹⁹ These will be described as Study I and Study II

STUDY I

Animals were selected at random from stray, mongrel adult dogs weighing from 15 to 20 pounds and excluding pregnant dogs, and dogs previously operated upon The abdomen was shaved, scrubbed and painted with iodine and alcohol Aseptic technic was rigidly observed Under intravenous nembutal sodium anesthesia, the abdomen was entered through a right rectus incision and the appendix drawn into the wound Mesenteric attachments were divided, and the appendiceal vessels were clamped, divided and ligated with silk In order to minimize a tendency toward intussusception, the appendix was ligated 1 cm from its base, with three coarse silk ties, rather than directly at its base The distal half of the appendix was then traumatized with a crushing clamp, the viscera replaced, and the incision closed in layers with silk No drains were used and no dressings applied Immediately after operation, each animal received 50 cc of castor oil by stomach tube

No attempt was made to withhold food or water postoperatively, and no intravenous fluids were given Temperature and leukocyte counts were determined every other day Necropsy was performed on all fatalities shortly after death All animals operated on are included in the series The animals that survived were examined not earlier than 14 days after operation Bacterial culture studies were made of peritoneal exudate in all animals A combination of antibiotics was not used in any of the treated animals, although it was recognized that their effectiveness might have been enhanced thereby The purpose of the study was to compare the results of the antibiotics individually Penicillin was not used in Study I

Ten animals were used as controls Of these, eight died of acute diffuse

peritonitis, six of them within the first four days. Two animals recovered, a survival rate of 20 per cent.

Ten animals were treated with streptomycin, starting 24 hours postoperatively and continuing for eight days. The dosage was 75 mg every six hours intramuscularly, a dosage equivalent of 300 mg every 24 hours. Of these, four died of peritonitis, three of them within the first six days. Six animals recovered, a survival rate of 60 per cent.

Ten animals were treated with aureomycin, starting 24 hours postoperatively and continuing for eight days. The dosage was 100 mg four times a day orally. Of these, only one animal died, this occurring as late as the ninth day. Nine animals recovered, a survival rate of 90 per cent.

Ten animals were treated with chloromycetin, starting 24 hours postoperatively and continuing for eight days. The dosage was 62.5 mg every four hours orally. Of these, two animals died, one on the fourth day and one on the eighth day. Eight animals recovered, a survival rate of 80 per cent.

TABLE II—(Study I) Comparison of the Survival Rate in the Treated and Untreated Animals

	No. Dogs	2 Day Survivals	4-Day [†] Survivals	8-Day Survivals	14-Day Survivals
Controls	10	8	6	4	2
Streptomycin	10	10	8	6	6
Aureomycin	10	10	10	10	9
Chloromycetin	10	10	9	8	8

All animals were autopsied as soon after death as possible, and peritoneal exudate culture studies made. In addition, all dogs that survived 14 days were sacrificed and culture studies made. Five control animals showed a predominance of *Escherichia coli*. Eight animals treated with streptomycin showed *Escherichia coli*, while only four treated with aureomycin showed this organism. It is interesting to note that of ten animals treated with aureomycin, eight showed various types of proteus organisms. All ten animals treated with chloromycetin showed *Escherichia coli*, while only two showed proteus organisms.

The comparative survival rates of Study I are shown in Table II. The results of bacteriological studies* of peritoneal exudate are shown in Table III. Note that only five of the ten control animals showed *Escherichia coli*, while eight out of ten animals treated with streptomycin, and ten out of ten treated with chloromycetin showed this same organism. Four control animals revealed proteus organisms, only two each of those treated with streptomycin and chloromycetin showed proteus organisms, while eight out of ten treated with aureomycin showed this organism.

* Grateful acknowledgment is made to Dr. Frank W. Hachtel, Professor of Bacteriology, University of Maryland School of Medicine, and Miss Audrey Funk, Bacteriologist, University Hospital, Baltimore, Maryland.

STUDY II

Rothenberg *et al* have suggested that a more effective method of producing peritonitis in dogs would be to combine excision of the spleen and omentum with the technic of Bower, Fauley *et al* as described under Study I

Under Study II, the same principles of technic were observed except for the following (a) In addition to isolating and ligating the cecum, the spleen

TABLE III—(Study I) Incidence of Bacteria Cultures from Peritoneal Exudate of Dogs, with Experimental Peritonitis

Organism	Incidence	Controls 10 Dogs	Streptomycin 10 Dogs	Aureomycin 10 Dogs	Chloromycetin 10 Dogs
<i>Escherichia coli</i>		5	8	4	10
<i>Gamma streptococcus</i>		4	5	3	3
<i>Proteus</i>		4	2	8	2
<i>Clostridia perfringes</i>		5	3	1	7
<i>Staphylococcus albus</i>		4	0	0	1
<i>Streptococcus viridans</i>		0	2	0	5
Beta hemolytic <i>streptococcus</i>		1	2	0	5
<i>Staphylococcus aureus</i>		2	0	0	0

and the omentum of each animal were excised, (b) Five animals were used in each series instead of ten, and the period of observation covered seven days instead of 14. This shorter period of observation was selected because we were interested in bacteriological studies of peritoneal exudate rather than survival rate. The survival study is shown in Table IV.

TABLE IV—(Study II) Comparison of the Treated and Untreated Animals in Experimental Peritonitis (Method as in Study I with addition of excision of spleen and omentum)

Group	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day
Control	5	5	4	4	3	3	3
Streptomycin	5	4	4	4	4	4	4
Penicillin	5	5	5	5	5	5	5
Aureomycin	5	5	5	5	5	5	5
Chloromycetin	5	5	5	4	4	4	4

Five animals were used as controls, of which three survived seven days. All five animals showed a generalized peritonitis at autopsy, and no tendency to wall off. Eight different types of organisms were cultured from the peritoneal exudate with a total incidence of 22 positive cultures.

In this same study (Study II) the effects of penicillin were observed, in addition to those of streptomycin, aureomycin and chloromycetin. All five animals treated with penicillin survived for seven days, and then were sacrificed. Two of these animals showed a diffuse peritonitis and three showed a well localized abscess without evidence of a diffuse peritonitis. Bacteriological studies of peritoneal exudate revealed four different strains of organisms. The total incidence of positive cultures was eight. Five of these showed a heavy

over-growth of *Escherichia coli*. This represents the maximum number of positive cultures possible to attain in this study for any specific organism.

Four animals treated with streptomycin out of a possible five survived seven days. Autopsy of the animal that did not survive showed a diffuse peritonitis. Of those that survived one showed a diffuse peritonitis and three showed localized abscess formation about the appendiceal stump without evidence of diffuse peritonitis. Bacteriological studies revealed four types of organisms with a total incidence of 11 positive cultures.

TABLE V—(Study II) Postmortem Peritoneal Findings

Group	Animals not Surviving 7 days		Animals Surviving 7 days	
	Diffuse Peritonitis	Local Abscess	Diffuse Peritonitis	Local Abscess
Control	2	0	3	0
Streptomycin	1	0	1	3
Penicillin	0	0	2	3
Aureomycin	0	0	2	3
Chloromycetin	1	0	4	0

All five animals treated with aureomycin survived seven days. Upon sacrificing, autopsy studies revealed two with a generalized peritonitis, and three with localized abscess without evidence of diffuse peritonitis. Four types of organisms were cultured with a total incidence of 11 positive cultures. This incidence is similar to that for streptomycin, although the strains of organisms cultured were different. Streptomycin and aureomycin each had only one positive culture for *Escherichia coli*.

TABLE VI—(Study II) Organisms Cultured from Peritoneal Exudate of Treated and Untreated Animals

Organism	Control	Strepto- mycin	Peni- cillin	Aureo- mycin	Chloro- mycetin
<i>Streptococcus hemolyticus</i>	3		1	2	1
<i>Streptococcus non hemolyticus</i>	3				3
<i>Streptococcus viridans</i>		4			
<i>Escherichia coli</i>	4	1	5	1	3
<i>Staphylococcus albus</i>	2	3	1		2
<i>Clostridia</i> group	5	3	1		4
<i>Proteus vulgaris</i>	2			4	2
<i>Streptococcus faecalis</i>	2			4	
Gram negative rod anaerobe	1				

In the series of animals treated with chloromycetin, four out of five survived. The animal that did not survive showed a diffuse peritonitis. In addition, the four animals that were sacrificed at the end of seven days also showed a diffuse peritonitis. Bacteriological studies of the peritoneal exudate were positive for six types of organisms with a total incidence of 15 positive cultures. *Escherichia coli* was cultured in three out of five instances and *Proteus vulgaris* appeared twice.

A diagnosis of peritoneal irritation, probably secondary to an acute appendicitis, was made. Exploratory laparotomy was advised but was refused by the patient.

She was given 300,000 units of penicillin immediately after admission. This was repeated in 12 hours.

Twenty-four hours after admission, her temperature was 101° F and abdominal rigidity was more marked in the right lower quadrant. She persisted in refusing operation. Penicillin was discontinued and she was given 1 Gm of aureomycin orally. This was followed by 500 mg of aureomycin every 4 hours. Approximately 14 hours later, her temperature was 99.5° F and leukocyte count was 17,000. She was subjectively improved. Abdominal tenderness had diminished.

Thirty-six hours after starting aureomycin therapy a mass could be palpated in the right lower abdominal quadrant, about the size of an orange. On the third day of therapy, she was afebrile and asymptomatic. Abdominal tenderness had disappeared and the mass had reduced in size. Leukocyte count was 11,000. She was discharged two days later, completely asymptomatic, at which time the mass in the right lower quadrant had become poorly defined. Follow-up has not been possible.

DISCUSSION

The evidence in Case 3 supported a diagnosis of a spreading peritonitis, for which exploratory laparotomy was indicated and advised. Following the patient's refusal of operation and lack of response to penicillin, she was placed on aureomycin. Crile has shown that response to penicillin in peritonitis takes three to four days, and Altemeier²⁴ has offered an explanation for this slowness of response. It is possible that the apparently rapid response to aureomycin is due to its ability to act against *Escherichia coli* as well as secondarily associated organisms.

A total of 13 patients with peritonitis, secondary to appendicitis, were treated by surgery and aureomycin, and three patients with presumptive evidence of peritonitis were treated by aureomycin alone, without a fatality.

In addition, three intractable urinary tract infections, each of which showed positive cultures for *Escherichia coli*, have been successfully treated with aureomycin. Two of the cases are included with Table VII, showing an analysis of the clinical results.

The third case occurred in a 60-year-old male following a left lower pelvic ureterolithotomy. During the course of a year he had repeated hospital admissions because of chills, fever, urinary frequency and urgency. During these admissions he had penicillin, streptomycin and sulfadiazine respectively, without appreciable influence. He was placed on a course of 250 mg of aureomycin every four hours for eight days, after which bacteriological studies of the urine were negative. He has remained asymptomatic during a five month follow-up period.

Table VII shows the surgical conditions treated with aureomycin, and Table VIII, the types of bacterial organisms cultured.

Chloromycetin has not been given a clinical trial from the surgical viewpoint except in lymphogranuloma venereum. In this condition it will probably compare in value with aureomycin. Experimental data thus far obtained does

not warrant its clinical use in peritonitis. In infections involving proteus organisms, it should prove to be of merit.

Ochsner and Johnston²⁵ have estimated that in cases of appendiceal peritonitis treated conservatively, three-fourths will subside spontaneously without going on to abscess formation, and that in the remaining 25 per cent incision and drainage of the abscess will be necessary.

TABLE VII—*Clinical Studies*

	No Patients	Diagnosis	Av Age	Av Hospital Days	Results	Mortality
Non opera- tive Cases	3	Acute appendicitis	30	5 66	Excellent	0
	2	Acute perforated appendicitis walled-off abscess	44 5	9 9	Excellent	0
Operative Cases	11	Acute perforated appendicitis generalized peritonitis	19 42	14 9	Excellent	0
	1	Perforated sigmoid diverticulitis generalized peritonitis	52	11	Cecostomy and drainage	Died
Post- Operative	1	<i>E. coli</i> cystitis gastric ulcer	74	19	Asymptomatic	Died from severe gastric hemorrhage
Genito Urinary Infections	1	<i>E. coli</i> cystitis and peritonitis following uretero sigmoidostomy	72	39	Excellent	0
Total	19		23 40	11 21		10 5%

Crile, in discussing a series of cases of peritonitis of appendiceal origin, reported 23 cases that were treated successfully with penicillin alone. Four days of therapy with penicillin was adequate to control the average case. Of the 23 cases reported, 20 subsequently had an interval appendectomy with confirmation of a gross perforation of the appendix.

TABLE VIII—*Organisms Cultured from Clinical Cases*

Organism	<i>E. Coli</i>	<i>B. Hemolytic Strept</i>	<i>Strept Viridans</i>	<i>Cl. Welchii</i>
Number of cases	10	2	1	1

It has been stated by several observers that *Escherichia coli*, in pure culture is not a pathogenic organism but is in reality a saprophyte and that in mixed infections, the gram-positive cocci are the chief offenders. Since penicillin does not inhibit the growth of *Escherichia coli*, its effectiveness in peritonitis is probably due to its ability to control secondarily associated organisms.

Altmeier has shown that cultures of *Escherichia coli* or of *Bacillus pyocyaneus* have the property of destroying the activity of penicillin. This ability could well account for the fact that large doses of penicillin are required to

control gram-positive cocci when they are growing in a mixed infection associated with *Escherichia coli*

The treatment of peritonitis of appendiceal origin with antibiotics should not be construed as a substitute for surgery. Our series of patients is too small to be of clinical significance. However, the experimental and clinical results obtained suggest that aureomycin has a protective mechanism in peritonitis of appendiceal origin. A combination of penicillin and aureomycin therapy should be extremely effective in the treatment of peritonitis of appendiceal origin in those conditions, where for one reason or another surgery is either contra-indicated or physical (environmental) conditions preclude its possibilities. As a dual adjunct in the surgical treatment of peritonitis of appendiceal origin, it should further reduce the present mortality rate. If sufficient aureomycin is given to destroy the *Escherichia coli*, it is possible that smaller doses of penicillin would be effective.

SUMMARY AND CONCLUSIONS

1 The clinical applicability of chloromycetin and aureomycin is reviewed. The major field of their usefulness appears to be in the treatment of infections with rickettsiae and certain of the virus group, and gram-negative infections.

2 Experimental peritonitis has been produced in a series of dogs in an attempt to compare the protective significance of aureomycin and chloromycetin with streptomycin and penicillin.

3 Experimental animals in Study II treated with either streptomycin, penicillin or aureomycin showed a tendency to develop a localized peritonitis. Control animals and those treated with chloromycetin did not show this tendency.

4 Additional experimental studies with chloromycetin and in larger doses, should be made before its clinical trial in peritonitis of appendiceal origin.

5 Smaller doses of penicillin would probably be adequate in the treatment of mixed infections involving *Escherichia coli*, when combined with aureomycin.

6 Since aureomycin is extremely effective against *Escherichia coli*, as well as most strains of gram-positive cocci pneumococci and hemolytic streptococci, further studies may prove it to be the antibiotic of choice in the treatment of peritonitis of appendiceal origin.

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DISCUSSION—DR WILLIAM A ALTEMEIER Cincinnati Ohio Most surgeons agree that modern chemotherapy has been of great value in the treatment of acute septic peritonitis There is, however, no agreement as to the most effective antibacterial agent As yet, there is no specific treatment for peritonitis and successful management depends primarily on early diagnosis and prompt surgical intervention A review of our clinical experience in a total of 1283 cases of acute secondary peritonitis during the past eight years reveals that the mortality was reduced approximately 60 per cent in the 398 cases treated with

penicillin or penicillin and sulfadiazine. In our experience, streptomycin has been definitely inferior to either penicillin or sulfadiazine in the treatment of this disease.

Experimental work has shown that acute septic peritonitis, secondary to lesions of the gastroenteric tract, is usually a synergistic infection produced by the cumulative action of the various intestinal bacteria, and that nonpathogenic bacteria may be of importance in increasing the virulence of others with which they are associated. We also believe that clinical peritonitis following perforated viscera is not primarily an infection caused by gram-negative bacteria, but a mixed or synergistic infection in which the gram-positive organisms are often and usually more important. Large doses of penicillin are effective in secondary peritonitis because of their inhibitory effect on the gram-positive aerobic and anaerobic bacteria and not because of their action on the gram-negative organisms.

More recently we have become interested in aureomycin and chloromycetin as potentially effective chemotherapeutic agents in peritonitis. Both agents possess antibacterial activity against gram-negative and gram-positive, aerobic and anaerobic bacteria. Our experience with chloromycetin in experimental peritonitis and in a limited number of clinical cases of acute secondary peritonitis suggests that this agent is an effective and valuable agent. As more practical means of administering aureomycin and chloromycetin parenterally are found, the effectiveness of these agents should be increased.

DR WILLIAM L. BYERLY, Jr., Baltimore, Md. - I would like to express appreciation for such an enlightening discussion by Dr. Altemeier. It is well understood that a secondary fecal peritonitis is the result of a symbiotic relationship of organisms from the lower bowel with a ruptured appendix postoperatively leading to other causes.

(Slide) On this slide are listed the predominating organisms in 14 operative cases of diffuse peritonitis just discussed by Dr. Yeager. It is noted that the most frequent organisms, the colibacillus and the hemolytic streptococcus, have been shown experimentally and in vitro to be very susceptible to aureomycin.

The microphilia *Streptococcus viridans*, as previously mentioned, is not as susceptible to aureomycin, as it is to penicillin, and in the patient, as Dr. Yeager just mentioned, it may have been best if we had used penicillin in conjunction with aureomycin.

Likewise, clostridia organisms have not been found susceptible to aureomycin. We have not been able to make any satisfactory sensitivity determinations of clostridia organisms to aureomycin.

(Slide) However, as shown on this next slide, we do know that penicillin is moderately effective against the clostridia group. This slide shows the comparative sensitivity of the organisms commonly found in peritonitis of appendiceal origin and those which we have found in our experiments. You will notice that the gram-positive organisms are very susceptible to both penicillin and aureomycin. Aureomycin and not penicillin is effective against the gram-negative rods of the coliform group. The clostridia group as well as the *Streptococcus faecalis* are more susceptible to penicillin than to aureomycin.

Another interesting factor is that chloromycetin is the only antibiotic that the proteus group is highly susceptible to.

Early in the day a member of the Association mentioned something about the effect of these drugs on pyocyanic infections. Although it is not a common organism found in peritonitis, we see a number of infections with this organism. In both clinical and experimental studies it has been shown that chloromycetin, as in proteus group, has an excellent effect on this organism.

Editorial . . .

POSTOPERATIVE DEATHS

A SIGNIFICANT FEATURE of surgical progress during recent years has been the progressively lower and lower case fatality rates attained in radical surgery of the colon and rectum, the stomach, the lung, the pancreas and duodenum, and other organs. In each case the mortality rates reported from leading centers were initially high, that is, from 25 per cent to 50 per cent, especially during early developmental stages of the work. However, with increasing technical perfection gained through specialized experience and team-work, the acceptable rates fell year by year. Dr. D. F. Jones, a skillful Boston surgeon who pioneered in the introduction to American surgery of the combined abdomino-perineal resection for cancer of the rectum, lost from immediate operative complications about one fourth of the first hundred Miles operations in his series, commencing in about 1912. Twenty years later, as he approached his retirement, he was able to point with pride to the loss of less than one twelfth of his last hundred cases together with a substantial increase in the resectability rate. This record was established without benefit of sulfonamides and antibiotics, without blood banks and the employment of massive transfusions, without anticoagulant therapy for prevention or treatment of embolic disorders, and without reliance upon a staff of trained residents—and stands as an example of what could even then be attained through the acquisition of wisdom and technical perfection by a conscientious surgeon working without a complex specialized hospital team. The gains of the past 15 years in pre- and postoperative care have not brought about substantial improvement over the best records attained by individual master surgeons of the previous era—but they have gone part-way to reduce the gap between the best and the average. Many teaching hospitals and surgical clinics can now report operative mortality rates of less than eight per cent in most types of major cancer surgery, with many of the operations being performed by trained residents who are only at the threshold of their professional careers. In fact, the provision of team-work through the graduated residency system is probably of major significance in recent progress.

There is some danger that an attitude of complacency toward the risks of major surgery may be developing, based on the assumption that adequate supportive treatment (often to be given by some assistant) will offset all of the technical imperfections of a poor operation. This attitude must be vigorously combatted in all of the centers of training, because, far from being satisfied with our present records, we must continue to strive toward the virtual elimination of operative fatalities. If we face the matter honestly, we should recognize that we possess at this time the *knowledge* and the *technics* to guarantee a better than fifty-to-one chance for survival to every patient subjected to major surgical procedures. That we do not yet meet this standard is

due more to human error in not applying all available knowledge than to the occurrence of events beyond possible prevention or control

Therefore, an important avenue for clinical research is the unremitting and exhaustive analysis of the factors contributing to each death which occurs as a consequence of the operation, rather than as a direct result of the patient's disease. If the death is due to the anesthesia, and fortunately such deaths are rare, there was probably a failure to maintain proper balance between oxygen intake and dose of anesthetic. If the death is due to shock, or renal or hepatic dysfunction, there was probably failure to provide adequate and proper hemostasis and/or blood replacement, or else the patient's pre-operative depletion was not sufficiently compensated. If a catastrophic embolus is responsible, we may have failed to recognize early phlebothrombosis in a peripheral vein and thus missed the opportunity to supply appropriate preventive measures. If death has occurred from pulmonary complications, we must ask ourselves whether we have given the patient the fullest benefits of tracheal suction, antibacterial therapy, the maintenance of full ventilation, and proper fluid management. If peritonitis or ileus has supervened, we must suspect technical errors at the time of operation, inadequate bowel decompression, or sins of omission or commission in connection with nutritional fluid, or electrolyte balance. Since in this day and age the patient will certainly have been saturated with antibiotic agents, omission of the latter will probably not have been a contributing factor.¹ This list of avoidable causes for operative deaths could be extended far enough to leave us with very few factors in mortality which are necessarily beyond our powers of control, but there are some areas in which active research should still be conducted, such as

- 1 Improvement in our understanding of the effects of anesthesia and operation on hepatic and renal functions and of ways of offsetting such effects

- 2 Better technics for rapid restoration of the debilitated patient so that the effects of operation will be better tolerated. A really complete parenteral feeding regimen, allowing up to 4000 calories per day, together with amino acids, and all of the necessary electrolytes and vitamins would be of great assistance to this end

- 3 Some means for preventing thrombotic complications without the necessity to resort to drastic anticoagulant therapy

- 4 Adaptation of methods of maintaining the stable state to the special requirements of aged patients.

However, the greatest need in this area of operative mortality is not for research so much as for insistence on education in, and consistent practice of *knowledge which is already available*. If it were generally known that two hospitals can exist within a radius of five miles in which the mortality risk for a major abdominal operation is approximately twenty times as great in one as in the other, there would not be as much self-satisfaction within the profession as there seems to be

The surgeon who frequently travels by plane may have experienced the disquieting realization that the responsibility of pilot to passenger is quite analogous to that of surgeon to patient. Without having had any basis for judging the pilot's personal qualifications for the job, apart from the position his employers have given him, the passenger has staked his life on the pilot's ability to apply his technical judgment and skill to the handling of that airplane. He is counting upon him to bring the plane successfully through any unexpected and dangerous situation which may arise in flight. Since it is said that 80 per cent of airplane accidents are due to pilot-error, it is essential that the pilot *make no mistakes*. A major difference between responsibility of pilot and surgeon is that the former shares directly in the consequences of his error or neglect, while the latter does not. The least the surgeon can do is to learn all he can from each failure, whether it be his or another's, and to keep to a minimum those mishaps which could be said to be due to "pilot-error."

By the same analogy the question might be asked as to whether the individual patient is any better able to judge the competence of a surgeon than is the passenger to select his pilot. In both cases selection must be based upon the judgment of competent examiners rather than incompetent consumers of the specialist's services. Here again the pilot is by circumstances allowed only one serious mistake, while the surgeon may commit many and not even recognize his own errors as such.

Research in factors contributing to postoperative deaths will go on, and succeeding years will undoubtedly bring many more advances to add to those already made. However, these technics will only be applied successfully by the surgeon who has not only been subjected to a long and disciplined training, but is also well enough educated in physiology and biochemistry to keep pace with the derangements which his more and more radical operations impose, and whose conscience requires him to give his best attention to the needs of each and every patient coming within his sphere of responsibility.

JOHN S. LOCKWOOD

EDITORIAL ADDRESS

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BOOK REVIEWS

THE THYROID AND ITS DISEASES, by James H Means, M D, Professor of Clinical Medicine, Harvard Univ, and Chief of Medical Services, Mass General Hosp 2nd Edition 1948 571 pages Philadelphia, J B Lippincott Company

This is a fine medical monograph. It covers in an orderly, superbly arranged manner the entire field of the thyroid and most of its relations with other parts of the body. With the same clear simple style that has always characterized Doctor Means' lectures, the volume traces the subject from the embryologic and phylogenetic development of the gland through the historical and contemporary evidence regarding the nature and action of its hormone, its interrelationships with other endocrine organs, hypothyroidism, hyperthyroidism, nodular goiters and thyroiditis in their various forms. It covers available experience in the use of antithyroid drugs and in the use of radioactive iodine. Coming from the clinic in which the latter material received its first clinical trial it may be regarded as especially authoritative on this subject.

The chapters on pathology by Dr Rulon W Rawson and the chapters on surgery by Dr Oliver Cope are likewise excellent and enhance the value of the book.

Throughout the work the conclusions show the penetrating mind and well balanced judgment of a great clinician. We are fortunate in having this remarkable presentation of Doctor Means' accumulated information and experience in the field of his major interest.

J E RHODES, M D

SURGICAL PATHOLOGY by Peter A Herbut, Lea and Febiger, Philadelphia, 1948

The author has undertaken an impossible task because in so small a volume it is obvious that the field cannot be covered. However, there is a surprising amount of information and the illustrations are, for the most part, excellent and well selected. The effort to correlate the clinical and pathological findings, and in particular, the diagnosis, treatment and prognosis, makes the book easy reading. The references at the end of each chapter in a large part make up for the necessary omissions in such an abbreviated text. This would make it, presumably, a valuable book for the surgeon not in constant contact with a laboratory of surgical pathology.

The greatest defect, which is partly born of the necessity for condensation, but not wholly, is the dogmatic manner in which the material is presented. There are some errors in fact some of which are quite striking, such as under carcinoma of the thyroid, the statement that "symptoms of thyrotoxicosis are present in from 13 to 34 per cent of the cases." The errors seemed to be chiefly in the clinical discussion. Nevertheless, they constitute a drawback, particularly when so categorically stated.

The volume could be used by students preferably as a quick reference rather than as a text. It certainly contains a wealth of material and considerable effort has been made by the author to indicate the frequency and the clinical importance of the lesions under discussion.

There are some omissions, notably the pathology of the adrenal, the peripheral nervous system—the author has deliberately omitted the brain and spinal cord—and some neoplasms, as for example, chordoma.

The author is to be congratulated for a current and working handbook of surgical pathology.

VIRGINIA KNEELAND FRANTZ, M D

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RADIATION BURNS, INCLUDING VOCATIONAL AND ATOMIC EXPOSURES TREATMENT, AND SURGICAL PREVENTION OF CHRONIC LESIONS¹

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A STUDY of the development, pathology, course, and treatment of radiation lesions was recorded¹ in May, 1949. Further work, including repair of atomic radiation lesions and the surgical prevention of chronic radiation burns, is reported here, with a summary of essential findings from the first publication.

The value of radiation therapy and x-ray examination is not underestimated, and no suggestion is intended as a directional approach to problems in the use of radiation in any form. It is hoped, on the other hand, that discussion of possible unfortunate ultimate results of radiation may lead to prevention, recognition and elimination of these burdensome troubles. It is further hoped that the suggestion of "changing" the skin in an involved area *before* serious trouble develops may lead to even wider application of radiation therapy and even more brilliant results (Fig 8).

Diagnosis of radiation lesions should be easy from appearance and histories. It is mentioned here only to suggest that the element of suspicion that such a lesion might exist has been lacking in some instances and progress of the trouble has continued, often with irritant forms of therapy being added. This occurs in doctors themselves as often as in any group.

Sources of burns are vocational, as in doctors (Figs 1 and 2) and dentists, therapeutic radiation, either in known huge dosage or accumulative small doses (Figs 3, 4, 5) as for acne, diagnostic, as in fluoroscopic examination, the lesions of which are frequently missed in diagnosis because of lack of history or lack of suspicion, commercial epilation (Fig 6), this being a source of damage that seems the most useless, and atomic radiation, either in laboratory or test workers, or, of course, victims in war time (Fig 7).

* Read before the American Surgical Association, St Louis, Mo, April 20, 1949

ACUTE BURNS

These result from large single exposures, or from exposures repeated closely over a short space of time, or from atomic radiation, and should have a conservative plan for their treatment, especially as far as amputation of extremities goes. Rest, sedation, prevention of infection, and alleviation of the severe pain are carried out, as well as grafting of open wounds as soon as it is felt that a free graft or flap will survive. For burns of known surface extent, early excision and repair may be done, but even in these instances there may be surrounding involvement by a chronic process that becomes apparent later.



A

B

FIG 1—(A) Fluoroscopic burns in surgeons fingers, fairly rapid development in three years' time. (B) Result of resection and repair with free split skin grafts. One operation. Function and freedom of trouble obtained and patient able to scrub for surgical work.

CHRONIC BURNS

The chronic burn is the type usually thought of, such as those seen in the hands of doctors. These result usually from repeated small exposures over a long period of years, and the lesions are always getting worse. Acute burns from single exposures may result in the development of chronic changes also, and for this reason, after subsidence of the acute stage, trouble still may be expected.

The lesion in the skin is dangerous because it is a progressive one with the ultimate stage of carcinoma being in sight—if the patient lives long enough. Doctor Wolbach studied *the pathologic changes* and reported them essentially as coagulation, atrophy, endarteritis of the small arterioles, a compensation telangiectasis, clotting of the dilated vessels which gives the "coal spots," epithelial activity to throw the "coal spots" off, which in time causes keratosis, ulceration, and finally, after a long continued wound stimulus, carcinoma. This course requires five to 25 years, but is always progressive.

RADIATION BURNS

The usual type of carcinoma is squamous cell, but basal cell growths and even sarcomas may occur. This slow irreversible process of continual epithelial activity, trying to cast out the intradermal foreign bodies of clots and necroses, is perhaps the closest approach we have clinically to an ultimate cause and development of carcinoma.

It is possible that the effect on the vessels on the venous side of the circulation is important also in the changes that become irreversible. This involve-

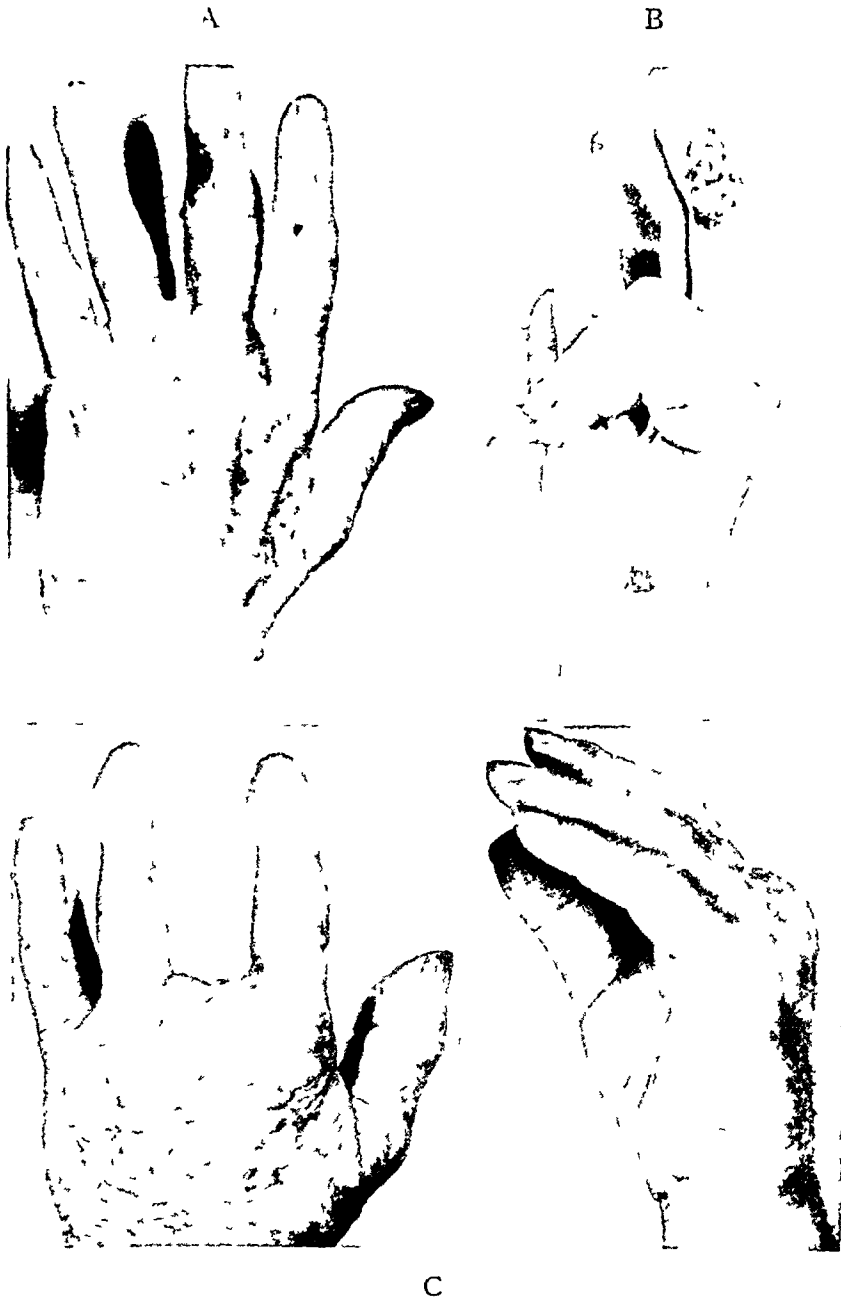


FIG 2—(A and B) Hands of surgeon (A S A) with vocational burn from disregarding his own safety in interest of patients, with carcinoma having developed in several areas. (C) Early result of wide deep resection and grafting, and of removal of finger that could not be repaired.

ment is of no special clinical significance, but is mentioned as an addition to the pathologic process recorded ¹

Effective treatment for the usual chronic burn is excision, and repair of the defects with free skin grafts or flaps. A paradox is that treatment should be done early, or in a quiescent stage, rather than in an ulcerated infected stage. This is hard to get even doctors to go through with, but if there is pain as well, this is an impetus to operation. Removal of the area results in immediate relief of pain, and the patient usually makes this escape the subject of his first

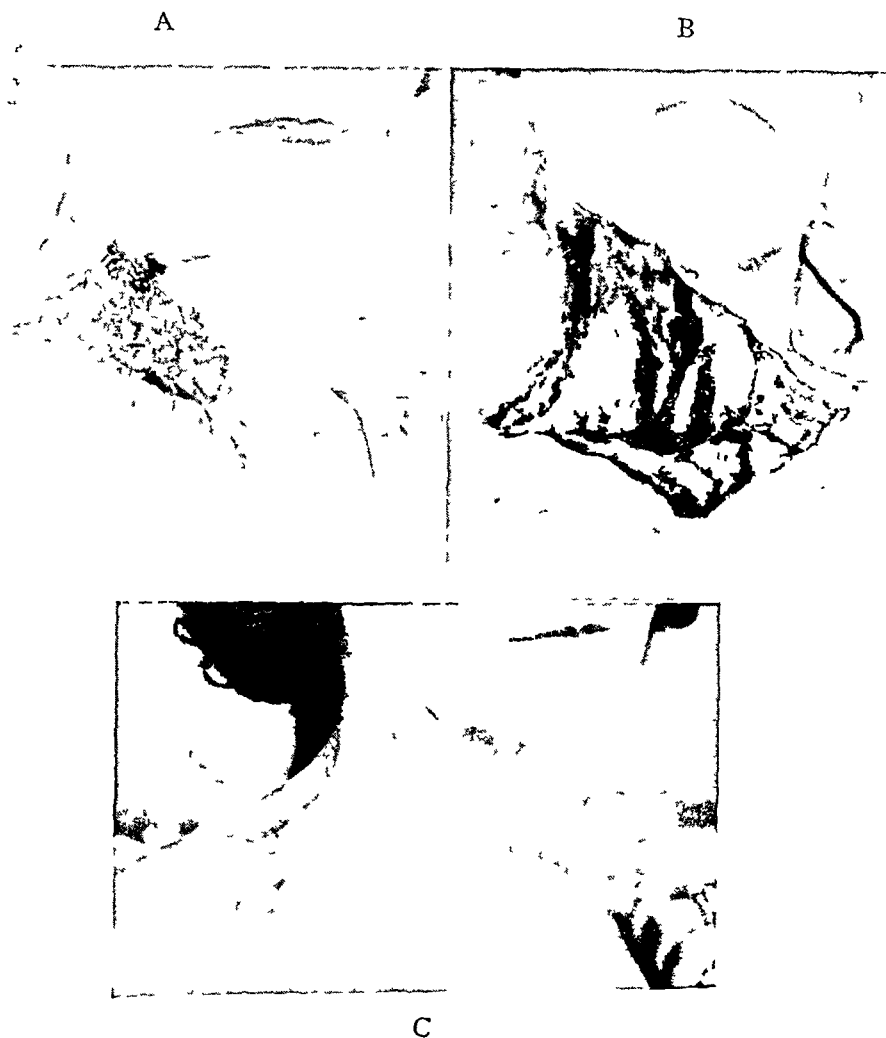


FIG 3—(A) Carcinoma in radiation burn from treatment of thyroid (B) Wide deep resection, including sternomastoid muscle and internal jugular vein, extending to trachea (C) Repair with pedicle flap from chest

expression on recovering from the operation. The repair of the excised lesion may be done either primarily or secondarily, and there are many points of importance in designing and carrying out repairs of these resultant open areas, especially when features are involved.

In hands, especially those of doctors where the fingers have to be dealt with, a conservative approach should be made in view of possible trouble with circu-

RADIATION BURNS

lation Both the palmar and dorsal surfaces should not be done at one time, and if the palmar surface does have to be done, great care should be taken with the blood and nerve supply in the dissection and in the dressing to prevent trouble It is imperative that at least one artery be maintained, and even then

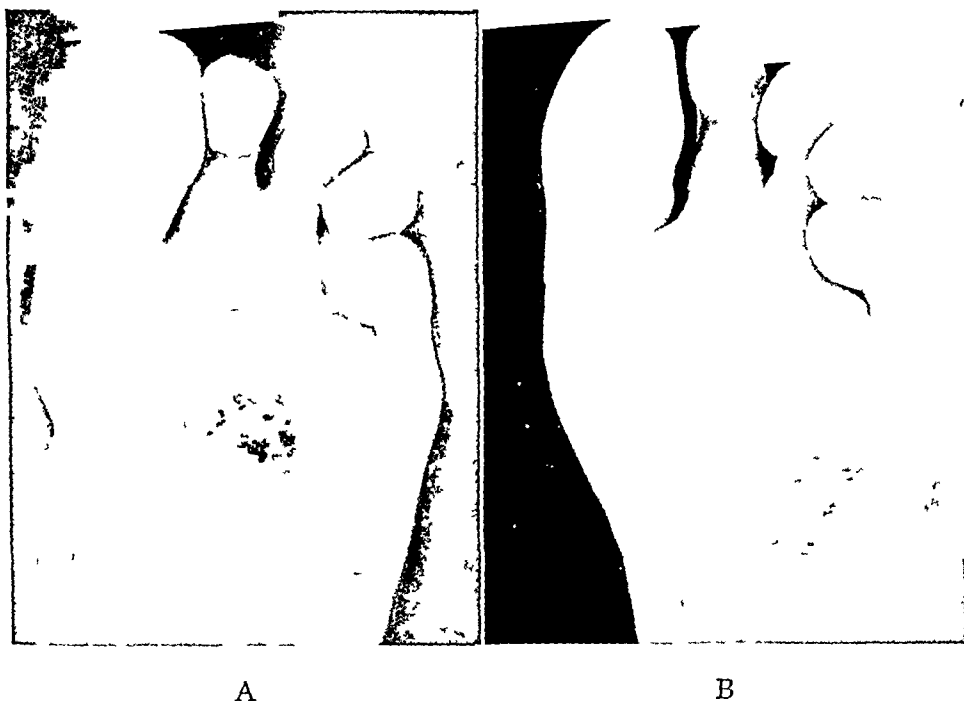


FIG 4—(A) Extensive change following roentgen ray treatment for plantar wart, with carcinoma having been removed previously from the burn (B) Result of wide deep excision and repair with thick split graft, one operation When there is sufficient soft tissue pad on the sole, free grafts can be used Otherwise, pedicle flaps are required

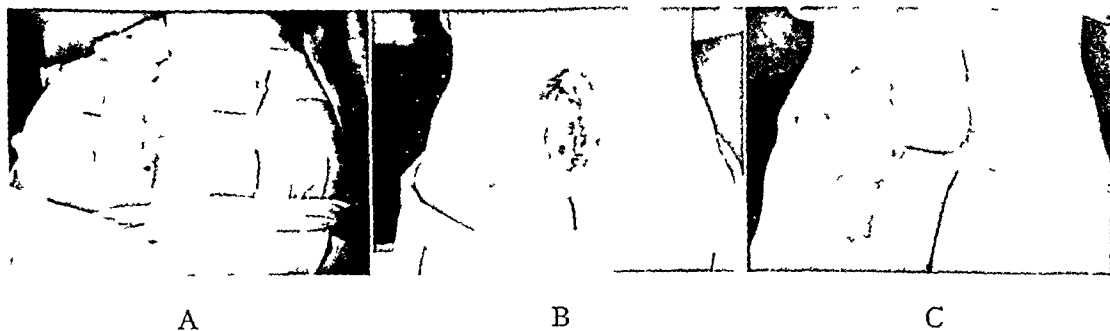


FIG 5—(A) Radiation burn following treatment for fibroids Spinous processes and ligamentum nuchae involved with excessive discomfort and pain (B) Resection without immediate repair because of exposed bone and ligaments Pain relieved (C) Repair with adjacent flap and grafting of donor site of flap

trouble with circulation may develop if there is sclerosis of the vessels beneath the excision

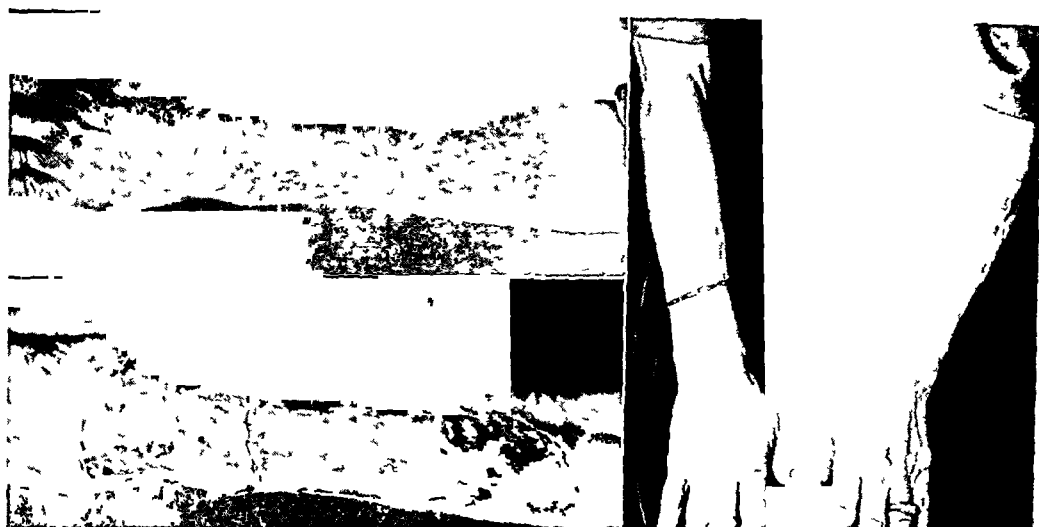
When there is known circulatory trouble present, it may be best to do cautery removal of isolated keratoses or ulcerations and allow them to heal individually A balance is that all possible fingers should be saved, but fingers

that have dangerous growths or hopeless function should be considered for removal

On the palmar surfaces the skin is so keratotic anyway that the typical gross appearance may be misleading and the diagnosis confused for excessive keratosis of other origin

The lesion, once developed, is irreversible as far as is now known, and further radiation of any form as treatment might have the term malignant applied to it. Occasionally, in late chronic burns with carcinoma already developed, some protective or temporary radiation might be directed toward the malignancy. If there is the possibility of alleviation of the carcinoma, this area

A



B

C

FIG 6—(A) Extensive roentgen ray burn following commercial epilation treatment (B) Immediate appearance following resection and repair with split grafts. One operation (C) Result 17 years later, showing normal appearance and persistence of function of the grafted skin

and the surrounding chronic burn can be treated surgically later, but this further radiation treatment is not recommended if excision can be accomplished primarily

Management of regional nodes where carcinoma has developed may be the same as for other carcinoma. These carcinomas do metastasize and small original lesions have proved fatal

Persistence of function in repairs after excision of chronic radiation burns usually occurs and the new skin covering lasts throughout life. The patient in Figure 6 is shown after 17 years, and may be expected to go on without further trouble, and others are known to be free of trouble over longer periods. It may be occasionally indicated to do secondary excision and repairs because of surrounding tissue change several years after what has been thought to be a satisfactory removal. This problem may have to be dealt with about the face,

where some limitation of excision may have been done originally to avoid damaging a feature

It may be found that there is too much deep fibrosis and necrosis to permit of immediate repair. In the popliteal region, to avoid nerves or vessels, and on the sole of the foot, especially in acute fluoroscopic burns, the excision may not be carried deep enough to arrive at an adequate minute blood supply that will carry either a free graft or a flap. These areas may be "dressed" with split grafts to get all possible take and finally be repaired later, or the areas may be left open. These points come under the statement above, that complicated problems of plastic reconstruction may arise.

Late necrosis of underlying structures such as bone and tendon may occur occasionally in severe burns and require excision, or amputation of fingers, as reported by Dr. S. L. Koch in the discussion of this paper.

Growth interference or failure of development to normal size of areas following radiation in infancy and childhood may occur, especially about the face. These areas may require replacement of overlying skin and restoration of features and this might come under the title of radiation burns, but problems here are essentially plastic surgery problems.

Chronic atrophy, whether diagnosed as a burn or not, will probably show up in practically every tumor area treated with radiation. If it were recognized that this might happen and that the atrophic skin should and could be changed, then some resistance to radiation therapy might be overcome.

Atomic radiation lesions may increase as work in turning mass into energy increases, and the incidence in the next war may be tremendous.

In time of war, fire and blast injuries may be greater in number than radiation injuries, but some of those surviving the blast and fire, and possibly many relief workers, will suffer radiation burns, and these lesions are under consideration here.

Enough burns have been encountered among workers in the development and production stage of atomic work to give indications of what to expect. The lesion produced by atomic radiation is not a new one entirely, but the time element of the development is faster than in the accumulative x-ray burn, due to the excessive exposure in a short space of time. These burns usually arise from mistakes in security precautions, and add the ever present human element to the ultra in scientific work.

Whether the radiation is Beta or Gamma may not be definite in some exposures, but as far as can be determined now the burns probably occur from both Beta and Gamma radiation. Because of excessive dosage, symptoms may begin very soon after exposure, and blistering may occur in four to six days. The blistering runs its course in about 30 days and there is either healing or sloughing, with resultant open wounds according to the degree of the exposure. Exposures heavy enough to be fatal are not for discussion here.

Conservative treatment, especially about the hands, avoiding early amputation, is indicated because hopeless looking fingers finally may be spared (Fig 7). Relief of pain, prevention of infection, and general supportive measures

are the main items of treatment. Blood changes are not significant in patients with exposures over small areas, but there may be emotional disturbances in workers that require patient guidance, with recreating of hope for ultimate survival of the damaged parts.

Since these accidents are apt to be of excessive local exposure, (12,000 r in a few seconds), more sloughing and ultimate atrophy may be encountered.

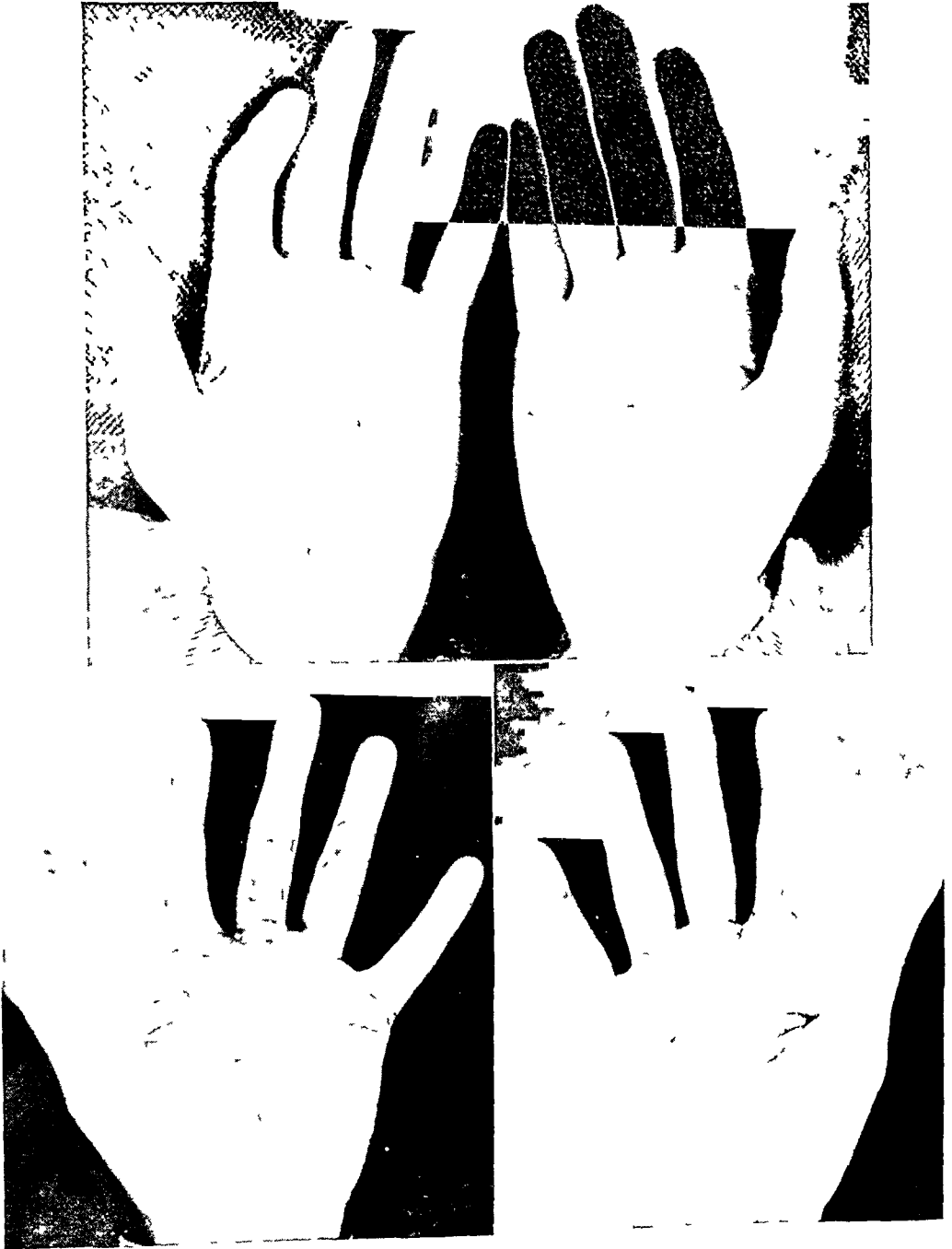


FIG 7—Examples of atomic radiation burns which have been treated conservatively in acute stages and are being repaired by resection and thick split skin graft repair.

RADIATION BURNS

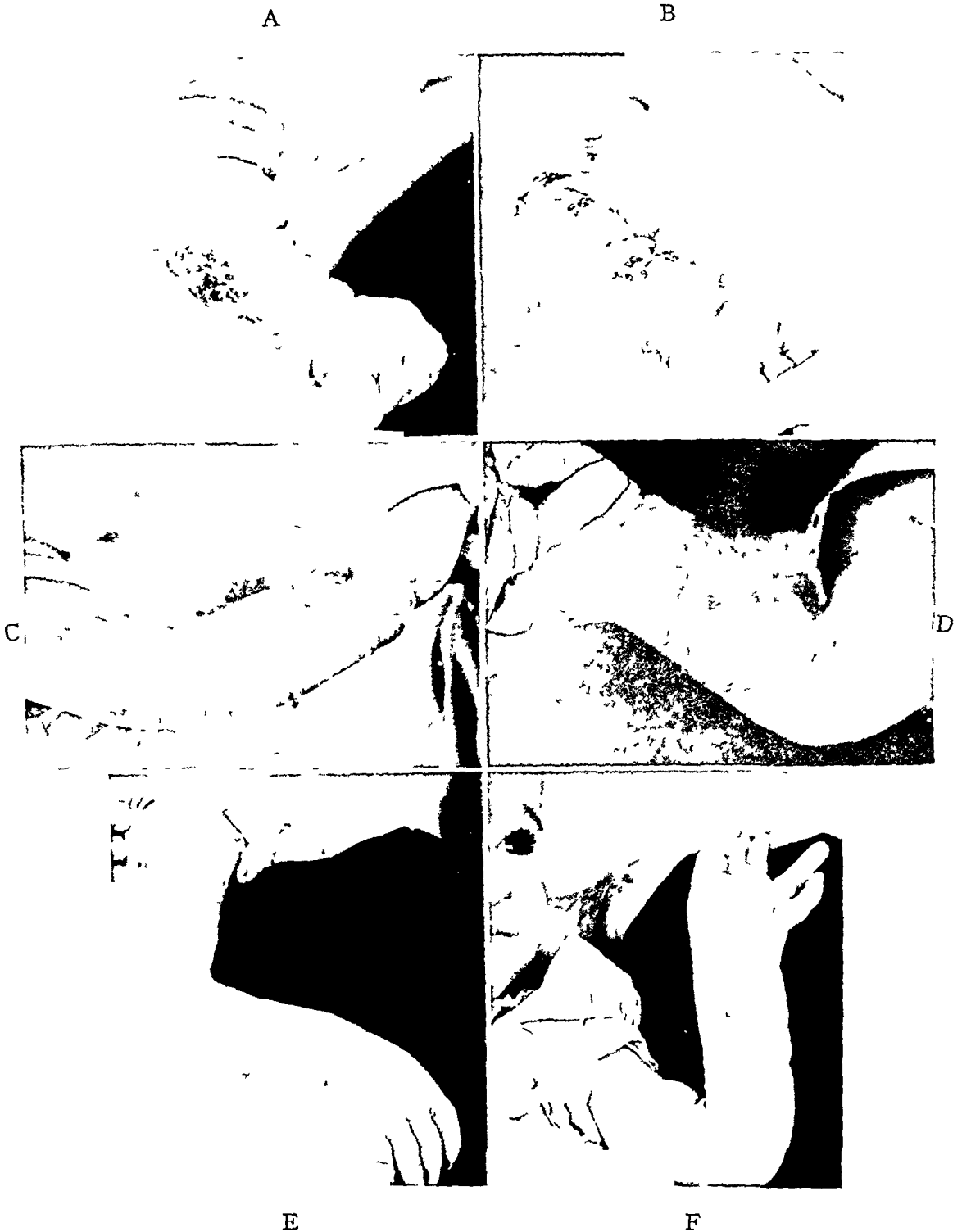


FIG 8—Prevention of chronic radiation lesion by resection and repair of area before chronic changes occur (A and B) Active arterial neoplastic hemangioma involving skin of entire arm Amputation had been recommended (C and D) Arm with control of the active hemangioma by x-ray treatment given by Dr W G Scott and Dr Sherwood Moore (E and F) Arm entirely covered with thick split grafts after resection of the skin which wasn't normal anyway, and which would have gone into chronic changes requiring removal Two operations

than in the usual x-ray burn, so that more amputations may be required. The pathologic processes may seem more contracted in time, that is, the various elements of tissue changes may develop faster than in the usual chronic radiation burn. This also is probably dependent on the large, sudden, single exposure. But these differences do not change the rule of being conservative in the acute stage.

The pathology seems to be close to that already described for radiation burns (with the added sloughing and atrophy) and for this reason, at least as far as the skin is concerned, the same idea of treatment of excision and grafting is indicated, but the burns are too recent to predict how soon carcinoma may be expected in ungrafted areas. It could be expected in ungrafted areas earlier than in the usual chronic radiation burns from accumulative exposures.

In summary for atomic radiation burns it may be said that they are probably similar in pathology to the usual radiation burn. The lesion in the skin is probably a progressive one after it is once established, and instead of getting better it will tend to get worse. Conservative treatment, especially in reference to amputation, should be carried out in the acute stages. When there is subsidence of the acute stage, open areas may be grafted to hasten healing. When the chronic stage develops and the lesion in the skin is troublesome and its progressiveness is recognized, the involved areas may be excised and grafted with free grafts or covered with flaps as indicated. Pain will almost always be relieved by operation, and the new skin in the area will probably survive without further change, unless there has been deeper damage that will undergo necrosis from failure of blood supply because of damage to the deeper vessels. After the area of the most acute burn is controlled by excision and grafting, there may appear later a chronic change in the surrounding tissues, and if this develops into a chronic radiation burn, the same process of excision and skin grafting can be followed as for any other chronic radiation burn. This is best carried out before too much ulceration has developed. Possibly some late amputations may be indicated, but the conservative rule can be followed.

Prevention of chronic skin lesions in heavily radiated areas may be done by excision and grafting *before* the chronic changes occur. The baby shown in Figure 8 had a total involvement of the right arm with an active neoplastic, arterial hemangioma. She was sent in with amputation recommended. It was known that the overlying skin was no good anyway, and it was thought that if the activity of the tumor could be stopped, then the skin could be changed before serious late lesions developed. X-ray treatment was carried out by Dr W. G. Scott and Dr Sherwood Moore, and the brilliant result shown in (b) and (c) was obtained without further activity of the tumor occurring.

The scarred skin of the entire arm was then resected, and replaced with thick split grafts in two operations, and the child has normal function and no further trouble. To all appearances, complete rehabilitation has been effected. This saving of the arm by radiation, and the prevention of the late bad effects of the therapy by surgical resection and restoration with skin grafts, is thought

to be of worth-while consideration, and possibly to open up wider fields of usefulness in the radiological management of serious crippling lesions

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Due to unforeseen difficulties, some illustrations of facial lesions were omitted at the time of publication of this article

DISCUSSION—DR ROBERT H IVY, Philadelphia A considerable proportion of the practice of the average specialist in plastic surgery is the repair of damage caused by irradiation—frequently, it is true, following justifiable treatment for cancer, but just as often for benign conditions where primary surgical treatment would have avoided this damage and rendered late secondary operations unnecessary in many cases

I can only confirm what Dr Brown and his associates have stated regarding the indiscriminate use of x-rays and radium for benign growths and inflammatory and other skin lesions This irradiation damage does not occur only in the hands of the inexperienced radiologist We have seen many cases from the clinics of men of the highest standing and experience

I believe much good could come from presentation of a paper of this type at one of the large radiological meetings, because many radiologists do not seem to be aware of these late reactions

The slides represent one or two cases of irradiation damage requiring excision of the lesions and secondary repair of the resulting defects

May I close by quoting the last sentence from an editorial in the Journal of the American Medical Association for September 18, 1948 (138 214, 1948), entitled "The Hazards of X-Ray" "Roentgen treatment for benign conditions should be used only with a vivid appreciation of its capacity for harm, and with an overt evaluation of its presumptive benefits weighed against the known and possible injuries inseparable from its use in effective dosage"

DR SUMNER L KOCH, Chicago I am sure every one of us would be happy to secure results such as Dr Brown and Dr Ivy have shown here In listening to Dr Brown's discussion of this problem and seeing his cases, I am always impressed with the difficulties and the serious problems which they present I am also impressed by the fact that none of these difficult cases are turned away, but that they are helped and often almost unbelievably improved

I would like to show two cases, the first an acute radiation injury much like that of the young doctor whom Dr Brown showed

(Slide) This patient came to us after having spent two days before Thanksgiving and the day after, examining fuses under a fluoroscopic screen She had spent a total of 24 hours at this work and came to see us ten days later

(Slide) At that time her fingers looked as though they had been extensively infiltrated with a local anesthetic They were red, white, over areas of greatest tension, and greatly swollen

(Slide) After about a week of daily dressings the sloughing skin separated

(Slide) We were able then to apply skin grafts over the raw surfaces

(Slide) The skin grafts healed kindly, and for two years the patient was able to continue her regular work Then she returned with degenerative changes beginning to appear beside the areas which had been grafted

(Slide) Since that time it has been necessary to remove the greater part of the distal phalanges of the four fingers of the right hand. On the lateral side of the thumb the bone is becoming exposed over the proximal phalanx, and we are still faced with the problem of further surgical work on this patient.

This case emphasizes the fact that the care of these cases is a continuing problem.

(Slide) A second type of case which has proved difficult for us has been the patient with injury of the ventral and dorsal surfaces of the lower trunk after excessive radiation for an abdominal tumor.

(Slide) This patient was treated by raising flaps from both buttocks and rotating them medialward. A part of the flap which was to cover the sacrum was lost, and it was necessary to complete the repair with free grafts. Healing has now persisted for two years. The fact that the radiation injury always extends more widely than is apparent from a surface examination adds to the hazard in raising and transferring a flap in these cases.

(Slide) A year after the first series of operations the irradiated area on the ventral surface broke down, and it was necessary to carry out repair of this area.

(Slide) This was accomplished by wide excision and covering of the raw surface with a single pedicled flap.

DR RUDOLPH MATAS, New Orleans. I cannot resist the temptation to join in this discussion, as x-ray and radium burns have a special appeal to the men of my time, in whom pioneering in x-ray and radium therapy was somewhat of an adventure involving risk to both the doctor and patient. Ignorance of the proper technic, lack of experience, and the universal curiosity to see the rays at work searching for lost bullets or foreign bodies, or the setting of broken bones, led to prolonged exposure of the patients in various parts, and of the doctors' hands, without adequate protection. It was only until many disasters, including amputations, hastened the development of a better technic that finally, as at present, the dangers of x-ray and radium burns have become practically negligible in competent hands. But the reports we have just heard show that notwithstanding all the improvements in radiology, the risk of late necrogenic dermatitis and malignant transformation of the irradiated areas still exists and is far from negligible.

I recall many young medical x-ray pioneers who suffered from x-ray burns of the hands caused by prolonged exposures without adequate protection, and it is in this group that the chronic radiodermatitis, followed by cancer of the fingers and hands, were most frequently incurred.

I am well acquainted with the young Spanish surgeon referred to by Dr. Brown. He was following a course in plastic surgery and availed himself of the opportunity to get rid of a chronic radiodermatitis which he feared was the precursor of cancer. I am pleased to confirm that Dr. Brown's excision of the affected areas, followed by grafting, has yielded excellent results, physiologically and cosmetically, leaving the fingers and hand free to perform the most delicate plastic operations. The fingers of the opposite hand, showing a marked tendency towards subsidence of the eruption, were not operated upon.

Incidentally, x-ray and radium burns are exceedingly painful, and I do not believe anything exceeds the constant torture of a radium burn. The relief of pain is therefore a great problem in dealing with x-ray and radium burns. Extirpation of the burned areas is the most certain mode of obtaining relief, but the practice of excision was not generally adopted until about 1908 and 1909, when Charles Allen Porter of Boston began his advocacy of excision in precancerous lesions. But extirpation is not applicable to all cases, especially those involving certain widely spread and vital areas. Innumerable formulas were devised and tried, almost all the effective ones ending in mixtures containing opium. It is interesting to recall, however, that one lotion did, unexpectedly,

come to the rescue after a long gamut of soothing and healing dermatological applications had been tried and failed. This remedy was the so-called "Fisher Fluid," which I first saw announced in the London Lancet of October 29, 1913. It is named after Dr. J. L. Fisher, Director of the Municipal X-ray Clinic at Copenhagen, Denmark. It is purported to be a compound of horse serum treated with Trypsin, freed from coagulable substance, *horse saliva* and $\frac{1}{2}$ of 1 per cent carbolic acid as a preservative. This fluid, which became known in the trade as "incitamin," had a very considerable circulation in America, once its soothing and healing properties became known. It was applied to the diseased surfaces on gauze compresses soaked in the fluid, the gauze kept always moist. The second world war interrupted the importation and the manufacture in this country. It was claimed that incitamin was a specific. It certainly relieved pain and aided as nothing else did.

One of the most terribly impressive and distressing examples of the cruel and deadly effects of the x-rays when applied in massive (brutal) and prolonged doses and delivered at a short distance upon an unprotected surface, was that of a young woman from Vicksburg who had been treated for a small non-toxic goiter by an ignorant and unscrupulous quack. This happened in the winter of 1898, close to the beginning of the Roentgen era.

When I was called to see this patient she was practically moribund, in a stupor from a profound toxemia and marasmus caused by an acute necrotic laryngo-pharyngitis, with almost total obstruction of the air passages compelling an emergency tracheotomy, and an acute inflammatory stricture of the pharynx and upper esophagus, blocking the way to all food and drink. Widely diffused radio-dermatitis had spread over the neck from the chin to the sternum. The skin was intensely cyanotic about an incision to evacuate pus, plus a necrotic laryngeal cartilage. Pneumonia, with edema of the lungs, fortunately brought on an early end to this fearful, gruesome pre-cadaveric picture.

Another phase of the x-ray problems which still remains as a sequel to therapeutic radiation—the predisposition, or transformation, or metaplasia of radiated tissue, to cancer, the "x-ray cancer"—is tragically and most impressively told in the story of Dr. E. K. of New Orleans, one of the dental profession's most distinguished leaders, and the first in the world to demonstrate the enormous diagnostic value of the x-ray in dental practice (1896). Dr. K. had begun experimenting with x-rays almost immediately after Roentgen's epochal discovery (1895). Dr. K., though one of the greatest masters of x-ray technic, shared the fate of his early radiologic contemporaries, who, in exposing their hands freely to the rays, developed a radio-dermatitis which predisposed to malignant infiltration, which in this case began at the finger tips of the left hand and spread from one finger to another and then to the hand, compelling the amputation of these parts. But this was only the beginning of a series of amputations which followed in quick succession from the hand to the forearm and up the arm to the level of the armpit. In all, 35 operations were performed. Finally, when malignant ulcerations began at the stump of the arm he began to cough and expectorate blood. This was the last line of defense. All the signs announced that the vital citadel had fallen in the hands of the enemy. He had endured the pain and the continued distress of three years of suffering. He had reached the limit of endurance, and, though a tremendously courageous and determined man he could go no further, and on the morning of May 7, 1928, he was found dead in his office with a bullet through his brain. That is how this heroic sufferer put an end to his martyrdom and found relief.

Strange as this paradox seems of the subservience of radiation to cancer, it is more easily explained than the, at one time, mysterious process by which the tissues—after having been successfully x-rayed for the prevention of recurrence after operations for malignant disease, or further prophylactic purposes—retain a necrotizing potentiality in the radiated areas which does not manifest itself until the lapse of months or years, even three and four years, after the prophylactic rays have been applied.

This, fortunately, is not a frequent phenomenon, though it is always possible when we understand the mechanism of its production

As far back as 1923* I reported two cases of this delayed or latent type of x-ray burns (necrogenic radioactive dermatitis) which deserves more general recognition than it has received

In one case, a young woman, Miss A B, 25 years of age, was treated by radiation for a small toxic goiter. The patient was treated cautiously and serially at long intervals by an expert, the treatment being discontinued with the first appearance of an erythematous blush. All x-ray treatment ceased as the patient, after three months of intermittent radiation, was apparently completely recovered and well. At the end of four years of apparent cure and good health, a peculiar progressive dermatitis made its appearance in the neck, extending from the chin to the sternum and, laterally, to the clavicles. Necrotic patches and sloughing areas began to appear along the whole surface of the radiated area, which became very foul with ichorous discharges coincidentally with these local lesions, and the patient began to develop septic symptoms, delirium, fever, and stupor, with loss of vesical and rectal control. The secretions from the slough were particularly offensive. With these evidences of a profound toxic state Dr S, the attending surgeon, decided after consultation, to excise the entire diseased area, doing this in several sections. The patient immediately began to improve, and by the end of the ninth week was allowed to return home with her mind completely restored. The wound was slow in healing but it finally yielded to extensive and repeated grafting. Seven years after a complete recovery she married and continued well.

In another patient, a widow of 58 years, the outcome was not so favorable. After undergoing a very sweeping mastectomy on Halsted lines she remained apparently well both locally and constitutionally for three years (1903-1907), when a diffuse sloughing dermatitis appeared over the field which had been prophylactically radiated after the operation. The dermatitis appeared in patches, which gradually coalesced, leaving a vast surface of grey putrid skin which on removal left a foul grey area of unhealthy granulations and exudates, and which resisted all efforts at healing, or grafting. A radical extirpation of the entire surface of the left pectoral region was impossible, as it would have necessitated a solid resection of the entire thickness of the chest wall without any available skin flaps to cover the vacant space. This patient died 18 years after the original appearance of the delayed x-ray burn. The history of this patient was one of a long series of complications and vicissitudes, the death caused by prolonged suppuration, inanition, general cachexia, and exhaustion.

[*Added commentaries since the discussion by Dr Matas*] The detailed story of this patient was given in a discussion previously referred to in the *Am Surg Trans* for 1938.

The pathogeny of this type of long-delayed burns was fully explained in a paper by Dr Karl Grasman of Munich in 1923 (*Deutsch Zeitschrift für Chirurgie*, 149: 115, 1923). In this case Grasman reports the appearance of an x-ray ulcerative dermatitis which appeared four years after the patient had fully recovered from a fibro-myoxoma of the uterus which had been treated by x-ray radiation. The necrotic and ulcerated areas in the lower lumbar region and buttocks had resisted all forms of treatment until the diseased necrotic area was totally extirpated. After this was done complete recovery followed, fully confirmed two years after the operation. Professor Duerck, who made a very thorough study of the radiated tissues, determined that the necrotic process was caused by a primary radiogenic proliferation of the vascular endothelium of the arterioles and capillaries of the radiated region, specially affecting the vessels of the derm and

* See R Matas, Discussion of paper on "X-ray Burns and Their Surgical Treatment" by C A Porter, MD and S B Wolbach, MD—in *Trans Am Surg Assn*, pp 462-467, Vol 41, 1923

subcutaneous connected tissues, leading to a progressive and fatal ischemia and nutritional disturbance of the radiated fields

In summing up the results of my observations and experience, I need only repeat the conclusions arrived at in the previously quoted paper read at the meeting of this Society at Rochester, Minnesota, in 1923, viz "that once an x-ray burn is confirmed and especially if it has advanced to ulceration, practically nothing will accomplish a cure but a total excision of the entire diseased area, that is, provided this can be covered with healthy well-nourished flaps or by grafting provisionally on a perfectly healthy base," and with the proper judgment and skill displayed by Dr Brown in his exhibit here today

THE CIRCULATION OF THE SMALL INTESTINE AN EVALUATION OF ITS REVASCULARIZING POTENTIAL*

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THE BLOOD SUPPLY of the small intestine is not a new field for investigation Andreas Vesalius,¹ in 1540, presented an interesting, and for that day, surprisingly accurate illustration of the small intestine and its blood vessels† (Fig 1) Since then our knowledge of the blood vessels of the small intestine has been greatly amplified Upon a few points which have long awaited clarification, many differences of opinion persist among surgeons Further, certain erroneous ideas, long since disproved, repeatedly recur in the surgical literature of today Hence, it seems worthwhile to review briefly some of the more outstanding contributions to this field and to summarize the results of additional investigations carried out in our own laboratories during the past ten years

The duodenum, obviously a part of the small intestine, has been well studied by Wilmer² and will not be considered in this paper which is concerned only with the blood vessels of the jejunum and ileum, that portion of the small intestine which lies between the ligament of Treitz and the ileocecal valve This area is supplied exclusively by the superior mesenteric artery, a branch of the abdominal aorta, and is drained by the superior mesenteric vein, a tributary of the portal system For purposes of discussion it is convenient to subdivide the blood vessels of the small intestine into two groups (1) Those vessels (extra-intestinal) which lie between the wall of the intestine and the superior mesenteric trunks, referred to as the *mesenteric vessels*, and (2) those which lie on or within the wall of the intestine, called *mural vessels*

Usual descriptions of the mesenteric vessels are in agreement so far as the larger arteries and veins are concerned This is to be expected, for they are of such size, and are so placed that their demonstration is relatively easy The vasa recta, and to an even greater extent the vessels within the intestinal wall, present much greater difficulties in study, usually requiring injections and other special technics As a result many discrepancies are to be found among the descriptions of these finer radicles of the intestinal circulation This

* This investigation was supported by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U S Public Health Service Read before the American Surgical Association, St Louis, Missouri, April 21, 1949

† The accompanying text describes the intestinal arteries arising from a large trunk from the aorta, giving off branches which branch in arborescent fashion to communicate with each other within the intestine Similarly formed veins are described as joining the portal system which leads to the liver

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emphasizes the fact that technic for vascular study must be carefully chosen for suitability to the problem, and the results critically analyzed if one is to avoid the hazard of contributing to misinformation rather than adding to knowledge

Dwight³ in 1898 described the human small intestinal vessels before the Association of American Anatomists, and published his findings in somewhat different form in the *Anatomische Anzeiger* in 1903.⁴ This is one of the earliest and best descriptions, brief but accurate, and he clearly recounts the characteristics of the arcuate vessels and observes that the vasa recta do not intercommunicate between their origin and the point where they join the intestinal wall. The classical papers of Monks^{5,7} are familiar to all surgeons, and added greatly to understanding of the increasing complexity of the arcuate system and greater amounts of fat in the mesentery in the distal portions of the intestine. Eisberg⁸ reported a most complete study of the small intestinal circulation in both man and the dog, and Cokkinis^{9,10} presented detailed findings based upon injection studies of human intestines.

Comparative studies of the small intestinal circulation were reported by Mall¹¹ who presented a thorough study of the dog with particular attention paid to the finer ramifications, by Bradley¹² who gave a brief but accurate account of the mesenteric vessels of the dog, and by De Blas¹³ who compared the branches of the superior mesenteric artery of dog and man, believing the latter to be better suited for efficient revascularization. Dieulafoy¹⁴ used radiopaque media for comparing the mesenteric vessels of the dog and rabbit. Morton¹⁵ published a most interesting comparison of the relative vascularity of the duodenum and ileum of the dog. Latarjet and Forgeot¹⁶ described the jejunal and ileal circulation of man, dog, cat, horse, pig and rabbit. One of us (Noer¹⁷) presented a detailed comparative study of the small intestinal circulation of man and certain laboratory animals. Much of this work is summarized later in this paper, as essential background.

Experimental mesenteric occlusion, a most useful technic for studying collateral circulation, has formed the basis for considerable investigation. The



FIG 1—The small intestine and its circulation as portrayed by Andreas Vesalius in 1543.¹

literature covering this phase of the problem was reviewed in a previous publication on this subject by Derr and Noer¹⁸ and will not be considered again at this time. Similarly, references to previous work on the effect of distention upon blood flow through the intestinal wall may be found in the paper on this subject by Noer and Derr¹⁹

TECHNICS

Anatomical studies of the blood vessels of the jejunum and ileum reported in 1943¹⁷ were based upon five human autopsy specimens and 29 specimens of 14 species of animals. Since then additional injections have been made in three rabbits, three dogs, two rats and two hamsters. Further, careful check upon the accuracy of the human findings has been made during the course of revascularization studies of 29 loops of human intestine. Thus the morphological descriptions detailed in this paper are based upon observation of 34 human autopsy specimens, nine dogs, five rabbits and 26 other animals.

Injection technics have formed the basis for conclusions as to morphology. Our earliest studies utilized the celloidin injection and corrosion technic described by Hinman, Morison and Lee-Brown²⁰. This provided excellent demonstration of the intestinal vessels, but the relationship of the vessels to the intestinal wall is not shown, so we rather early changed to the use of clearing technics after the method of Spalteholz²¹. Liquid latex, as described by Batson,²² proved to be an ideal medium for this. A modified combination of the technics of Batson and Spalteholz was described in detail in the 1943 publication¹⁷. The findings in cleared specimens in that report were checked by radiopaque injections of bismuth oxychloride after the method of Hill^{23, 24}. More recently specimens have been cleared in uncatalyzed polystyrene, then embedded in catalyzed polystyrene, cured by heat. This results in the most satisfactory method which we have yet encountered. The transparent plastic mounts are permanent, nearly unbreakable, and provide specimens equally suited to gross or microscopic study.

Mesenteric occlusion experiments were carried out in dogs¹⁸. Three types of ligation were practised: (1) Intestinal arteries alone, in varying number, (2) arteries, veins and nerves, and (3) veins alone. Ligation in continuity was done in 38 dogs, but because of doubt as to completeness of interruption all experiments were repeated with double ligation and division in a total of 83 additional dogs. Autopsies demonstrated the results in dogs which succumbed, and those which survived were sacrificed for autopsy after 10 days.

For further investigation of the mode of revascularization India ink in bovine plasma was injected in additional dogs after selected ligations as above, and the findings recorded by slow motion cine-photography²⁵. The India ink in bovine plasma was chosen because its viscosity and particulate size approximates that of blood, because its osmotic pressure is such that edema and diffusion from the vessels does not occur, and because its blackness is ideally suited for recording by cine-photography the course taken by the medium. A close correlation was demonstrated between the length of loop which the animal

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would survive in life and that which could be filled by injection. As a result it was felt justifiable to use this approach for a study of revascularization in human autopsy material. In all, nine human loops were studied, together with 20 dog loops, 15 from the rabbit and seven from the opossum.

The effect of distention on the efficiency of the anastomotic mechanisms was studied by similar experiments after introduction of balloons into the intestine. Intraluminal pressures were recorded with mercury manometers, and were varied during the course of injection while results were recorded for repeated study by slow motion cine-photography. A total of 20 human autopsy specimens were utilized for this phase of the investigation.¹⁹

It occurred to us that a natural extension of this work would be the use of "Roux-Y" loops for determination of the degree of mobility possible with

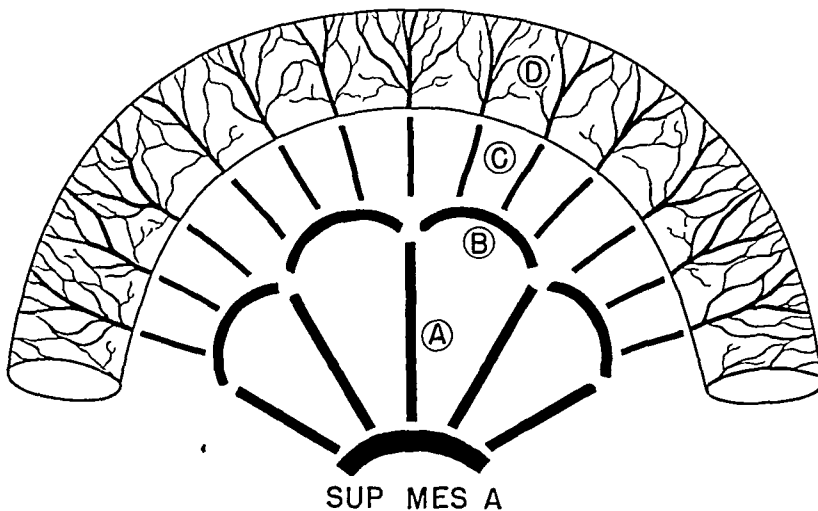


FIG 2 —Basic pattern of the small intestinal circulation. A Intestinal vessels, B Arcuate vessels, C Vasa recta, D Mural trunks and anastomoses

this procedure. It soon developed that this approach might also provide additional information as to the effects of distention upon partially devascularized intestine. The technique and results are detailed later in this paper.

RESULTS

Detailed analysis of the comparative morphologic findings appears in the 1943 report.¹⁷ Since then additional animals have been injected and many of the original specimens have been carefully re-studied with the aid of a binocular microscope with particular attention paid to the finer ramifications within the intestinal wall. Hence it appears desirable to restate some of these findings with slight changes in the finer details as viewed in the light of our subsequent studies.

The basic pattern of the small intestinal circulation is illustrated diagrammatically in Fig 2. All species conform to this basic plan though individual

variations are pronounced and at times even extreme as in the case of the pig. The superior mesenteric artery gives rise to a series of intestinal arteries which are joined by vessels which form the arcuate system. From the most peripheral of these arcades arise the vasa recta, smaller and shorter vessels which pass to the intestinal wall. Upon reaching the latter, they pass either to one side or the other of the intestine or bifurcate to send a branch to both sides. These vessels, now called mural trunks, pass into the wall of the intestine where they branch and anastomose freely with one another in a manner varying according to species. It is thus apparent that there are two principal anastomotic routes: (1) The arcuate system, and (2) the intramural anastomoses.

In man (Fig 3 a and b) the intestinal vessels vary in number between 12 and 16. The arches, simple and primary in the upper jejunum, increase in complexity in the more distal portions of the gut so that secondary, tertiary, quaternary and even quinary loops may be demonstrated. The vasa recta arise from the most peripheral arcades, and never intercommunicate between the peripheral arcade and the intestinal wall. Once the latter has been reached, however, the intercommunications between the mural trunks are abundant, in the jejunum and upper ileum by way of direct intercommunications passing obliquely along the wall, and in the lower ileum by a free plexiform type of anastomosis (See discussion of intramural anastomoses below).

The dog (Fig 3 c and d) presents a pattern varying considerably from this. Here the arcades are large, seldom become more than secondary or at the most tertiary and, for the most part, lie in close proximity to the intestinal wall. As a result the vasa recta are short and unlike those of man they abundantly intercommunicate, producing a free mesenteric border arterial anastomosis—a situation which does not exist in man. The intestinal wall of the dog is rather thick but the mural vessels show much fewer direct intercommunications than is the case in man, the majority of intramural anastomoses being through a plexiform type of intercommunication.

The dog has been described in some detail because of its considerable difference from the human pattern and because of its frequent use as an experimental animal. Other species have been described in the report mentioned above and it does not seem appropriate to include details in this paper. It is worthy of note, however, that most species show a resemblance to either the human or the canine pattern of mesenteric vascular morphology. Table I lists, by common name, the species which fall into these various patterns (See also Fig 4).

The anastomoses within the intestinal wall tend to be characteristic of species. Figure 5 shows the three types of intramural anastomosis most frequently seen (See also Figs 3 and 4). Type A, direct intercommunication between mural trunks by good-sized oblique vessels is characteristic of man, particularly in the jejunum and upper ileum. Type B in which the mural vessels break up into plexuses which then intercommunicate by much smaller anastomoses, is characteristic of the dog and of the terminal ileum of man. Type C shows arching intercommunicating vessels passing between the mural

trunks in an axis parallel to the long axis of the intestine This pattern is characteristic of the rabbit, to a lesser extent of the opossum and reaches its highest degree of development in the rat

The mesenteric occlusion experiments carried out in the dog¹⁸ revealed several interesting facts with reference to the ability of this animal's jejunum and ileum to withstand circulatory interruption. Contrary to previous reports, in this series interruption of any or all of the mesenteric supply to a 15 cm segment of dog's small intestine resulted in death of less than half the animals so treated. Also, contrary to the usual assumption, the venous ligations produced no higher mortality than interruption of any other vessel or combination of vessels. It was further shown that in this animal complete vascular deprivation of a segment 15 cm or less in length could not be accomplished uniformly by interruption of intestinal and arcuate vessels. This was considered presump-

TABLE I—Comparative Classification of the Jejunal and Ileal Vascular Patterns

"Human" Pattern ¹	"Canine" Pattern ²	Others ³
Man	Dog	Pig
Chimpanzee	Cat	Marmot
Opossum	Rhesus monkey	Sheep
Rabbit*	Raccoon	Goat
Wallaroo	Guinea pig	Rat
Hamster	Red fox	

¹"Human" pattern Well developed arcuate vessels relatively long vasa recta which do not intercommunicate, mural vessels joined for the most part by good-sized oblique vascular branches

²Canine pattern Relatively simple mesenteric arches which lie adjacent to the intestinal wall, short vasa recta which abundantly intercommunicate mural trunks joined by plexiform anastomoses

³Other patterns, Jejunal and ileal vessels intermediate between "human" and "canine" types (marmot and rat) or differing in marked degree from both (pig, sheep, goat)

* The rabbit shows occasional failure to complete its mesenteric arcades (Fig 4), hence has a less efficient revascularizing potential in these areas

tive evidence that some revascularization must occur by way of the intramural anastomoses. This study further showed no significant difference between the revascularizing potential of different levels of the small intestine

Additional studies²⁵ were undertaken in an effort to determine the exact means by which revascularization took place following mesenteric interruption. It was shown that there is a close correlation between the degree of vascular deprivation which dogs can survive and the amount of intestine which can successfully be filled by injection under similar circumstances. It thus appeared that injection technics might provide a suitable means for investigating revascularizing ability not only in the dog but also in man where ligation and survival experiments are obviously impossible. These studies revealed that approximately 15 cm is the maximum length of intestine which can successfully be filled with injection media after mesenteric vascular deprivation. Division of intestinal arteries alone resulted in filling of the interrupted arcuate

system from adjacent intact intestinal arteries. When interruption of the arcuate system at either extremity of the loop was added to division of the intestinal arteries, filling took place by way of vessels *within the intestinal wall*,

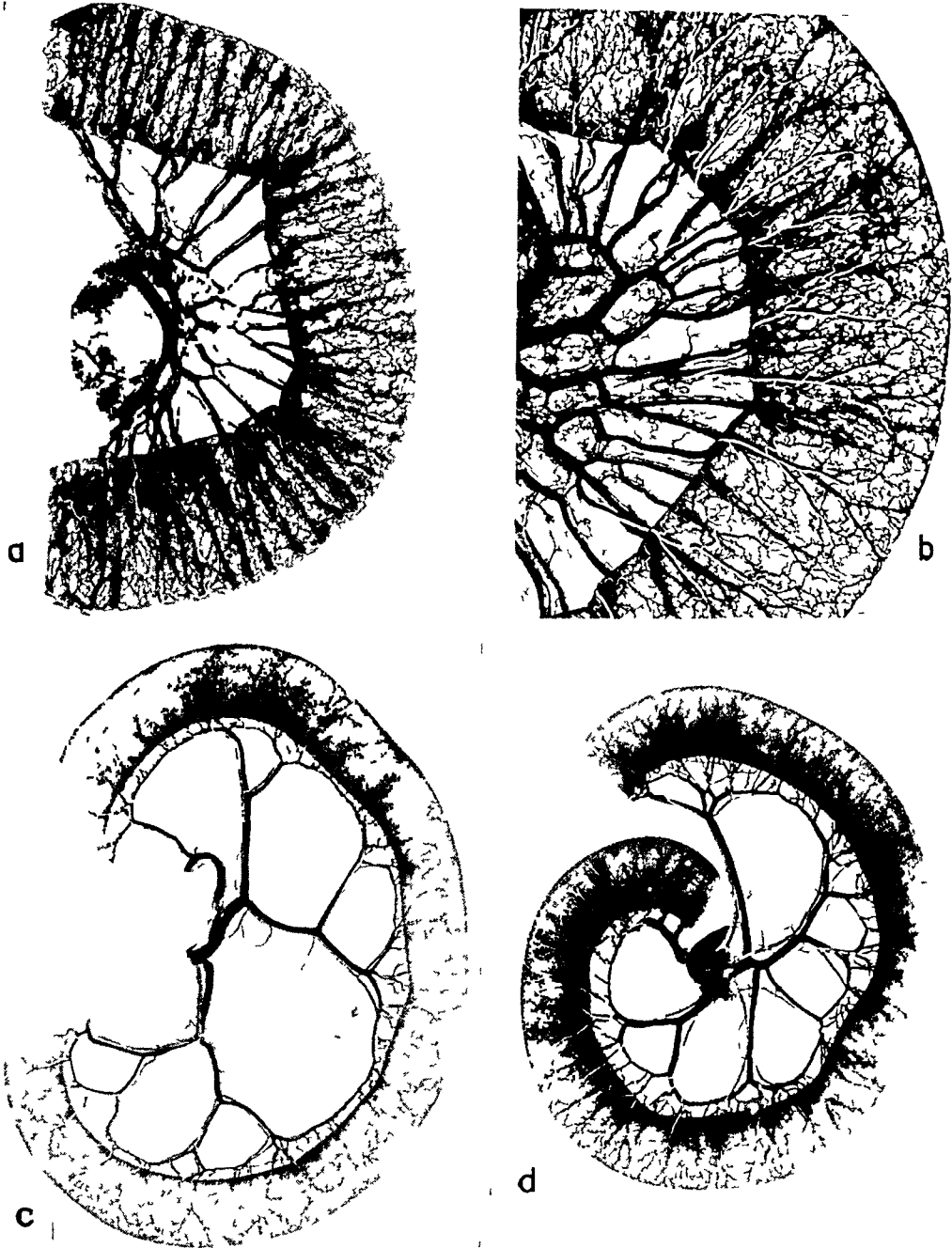


FIG 3—Photographs of latex injected and cleared loops of intestine. A Human jejunum, B Close-up of human ileum, C Dog jejunum, D Dog ileum

thence through the vasa recta into the isolated arcuate system and thence to the remainder of the loop through this arcuate system and its vasa recta. Surprisingly enough, interruption of the intestinal arteries and arcuate vessels

plus all of the vasa recta to the loop under study was followed by filling of the entire loop by way of the intramural vessels and their anastomoses. This occurred with complete regularity in man, opossum and rabbit. Only in the

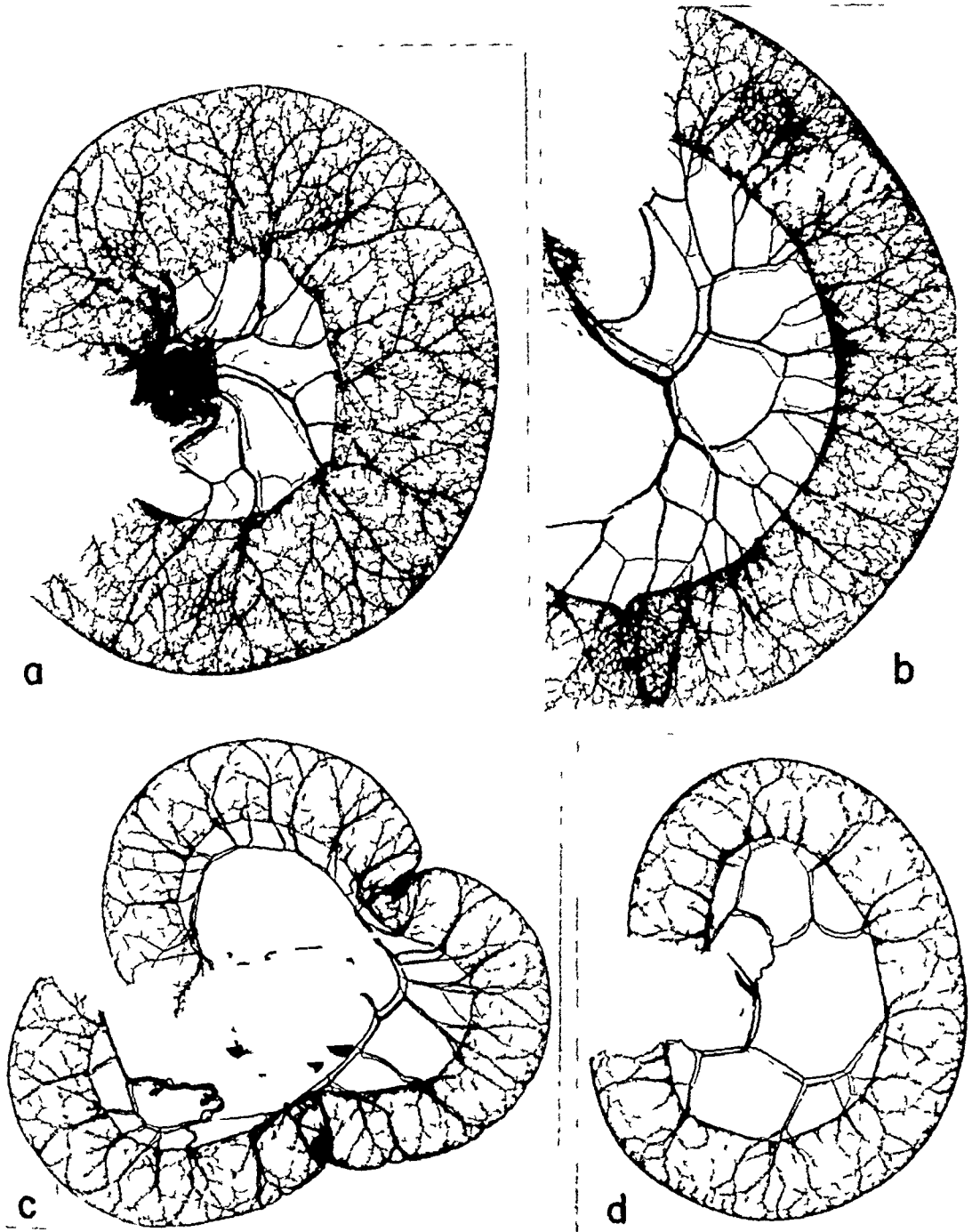


FIG 4—Photographs of latex injected and cleared loops of intestine. A Opossum jejunum, B Opossum terminal ileum, C Rabbit jejunum, D Rabbit ileum

dog did 15 cm loops occasionally fail of complete filling in their central portion. It was felt that this situation might be explained by the type of intramural anastomosis present in this animal, and it was this finding more than any other

which stimulated our re-study of the intramural anastomoses mentioned under morphologic findings

These results raised the question as to the possible influence which distention might have upon this revascularizing potential. The experiments just referred to were repeated after production of varying degrees of intraluminal distention¹⁹ and it was shown that pressures of 60 to 70 mm mercury prevented all intramural filling by injection, even with the mesenteric system intact. Filling of the larger intramural vessels occurred at 40 to 20 mm mercury but complete vascular filling occurred only in the absence of distention.

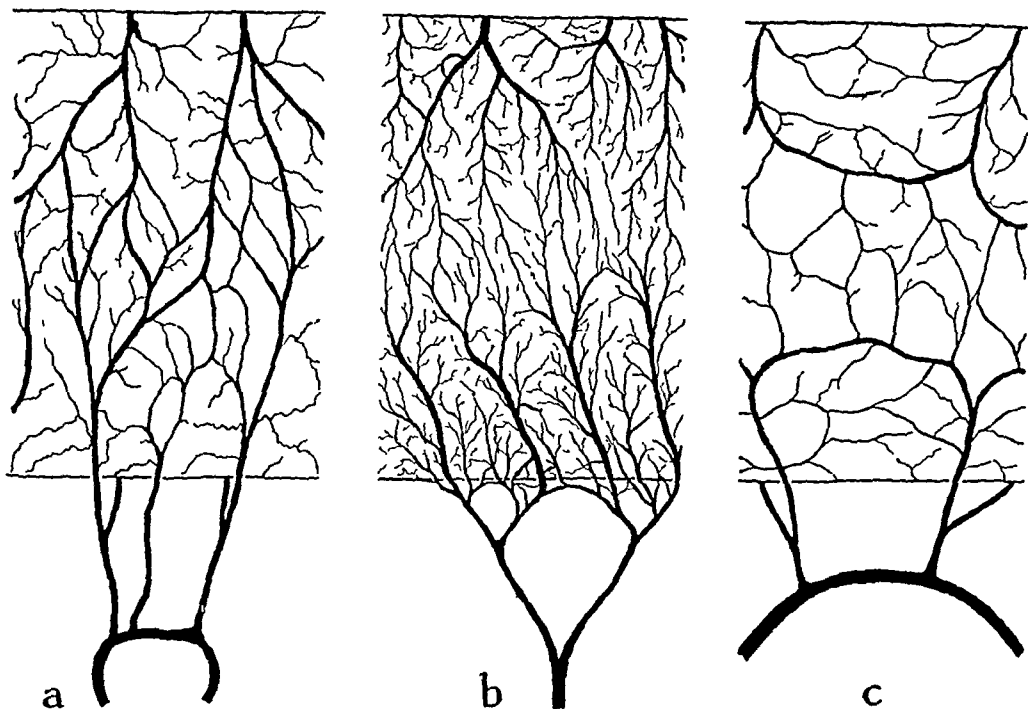


FIG 5—Types of intramural anastomoses (see also Figs 3 and 4) A Direct communications between mural trunks, e g, man B "Plexiform" type of anastomosis, e g, dog C Arching type of intercommunication, e g, rabbit, rat

In intestinal loops subjected to complete mesenteric vascular deprivation (*i e*, interruption of all vasa recta to the loop), filling of the deprived area by way of the intramural anastomoses could not be obtained until complete decompression had been accomplished.

"Roux-Y" experiments, not previously reported, have produced additional interesting data. Fig 6 is a diagrammatic representation of the procedure in the first series. The small bowel was transected 5 to 10 cm beyond the ligament of Treitz, and the distal end closed with a double layer of sutures. A 15 to 25 cm segment of intestine immediately distal to the point of transection was then freed by dividing the mesentery near its root but preserving its arcuate system. The proximal cut end was then anastomosed to the jejunum at the distal end of the free segment resulting in a typical "Roux-Y" loop, closed at its free

CIRCULATION OF SMALL INTESTINE

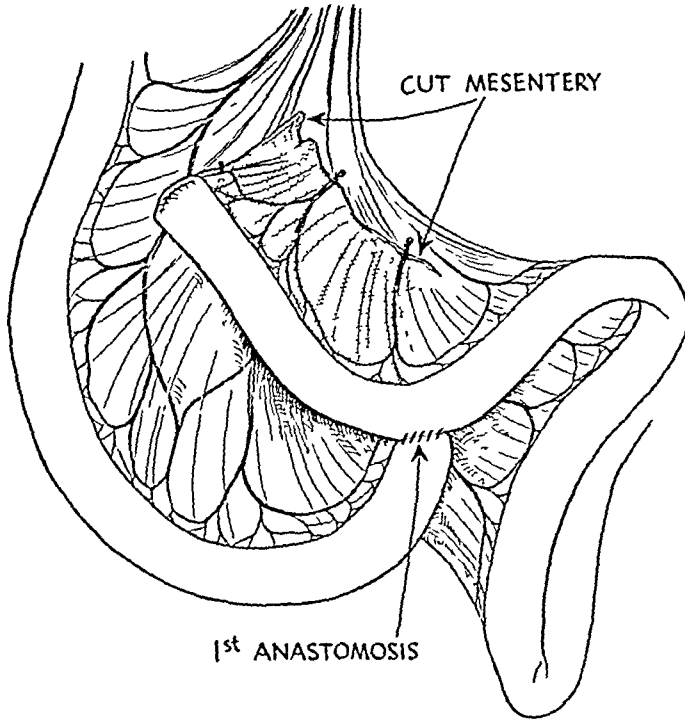


FIG 6—Diagram of procedure in first series of "Roux-Y" experiments

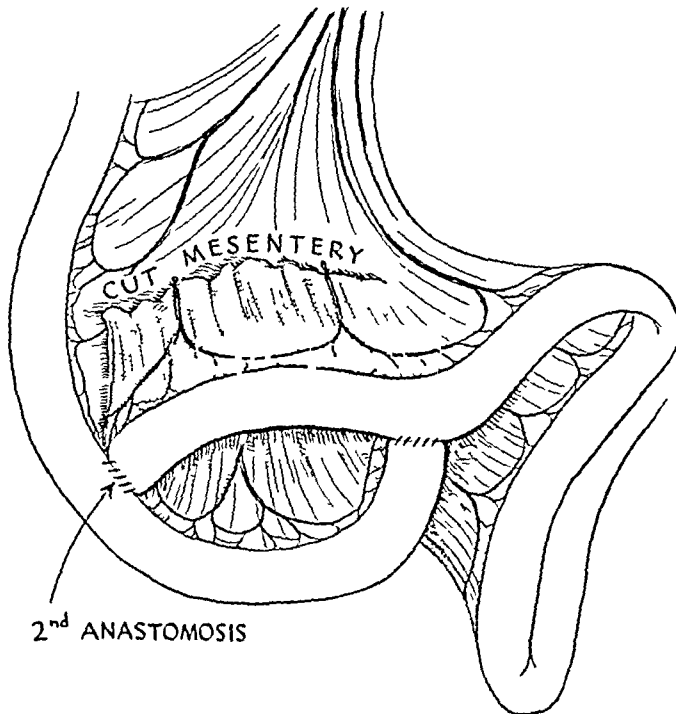


FIG 7—Diagram of procedure in second series of "Roux-Y" experiments (addition of proximal enterostomy)

end Seven dogs were subjected to this procedure Postoperatively all of these animals were severely ill, and all but one of them died within one to six days Postmortem examinations revealed the free loops to be dilated, gangrenous, and in most instances perforated One animal with a 25 cm loop survived after an extremely stormy postoperative course

The procedure in the second series of seven dogs is represented in Fig 7 Here, in addition to the "Roux-Y," a proximal end-to-side entero-enterostomy was also performed to vent the free loop into the intestine One animal with a 25 cm loop died on the first postoperative day Postmortem examination revealed no dilatation but a 3 cm area of infarction and perforation at the proximal end of the distal segment The remaining animals showed very little postoperative reaction, remaining alert and undistended, with good appetites They were sacrificed for autopsy approximately one month after operation The loop of gut in question was of comparable appearance to the remaining intestine, and the anastomoses were patent There was no evidence of distention

In summary, six of seven dogs in whom a "Roux-Y" anastomosis with a blind segment was performed died in from one to six days postoperatively with loops which showed dilatation, gangrene, and perforation The single animal which survived did so only after a protracted stormy postoperative course In contrast, six of seven dogs in whom the loop was decompressed by a proximal entero-enterostomy survived, and reoperation revealed the loops to be normal in appearance (See Fig 8)

DISCUSSION

The morphologic studies have clarified our understanding of the vascular pattern in the jejunum and ileum of man, and we hope they may correct some of the discrepancies to be found in the literature The comparative material has been briefly reviewed because of our firm conviction that too little attention is paid to species peculiarities in the choice of experimental animals There is far too widespread a tendency to select animals on the basis of convenience to the investigator rather than upon suitability of a given species to the proposed investigation The almost universal selection of the dog for experimental work upon intestinal obstruction and its circulatory disturbances is an outstanding example of this point The mesenteric circulation of this animal is perhaps somewhat more abundant than that of man from whose pattern it differs markedly The intramural circulation, on the other hand, appears to be definitely less efficient to such an extent as to require considerable care in the interpretation of results obtained from the use of this animal The opossum and the more readily available rabbit both resemble man far more closely with respect to both the mesenteric pattern and the intramural vessels Our subsequent studies herein reviewed thus lend further weight to one of the statements expressed in our 1943 paper "These conclusions emphasize the fact that if findings are to be applied to man the experimental animals should be chosen only after careful investigation has shown a somewhat similar morphologic

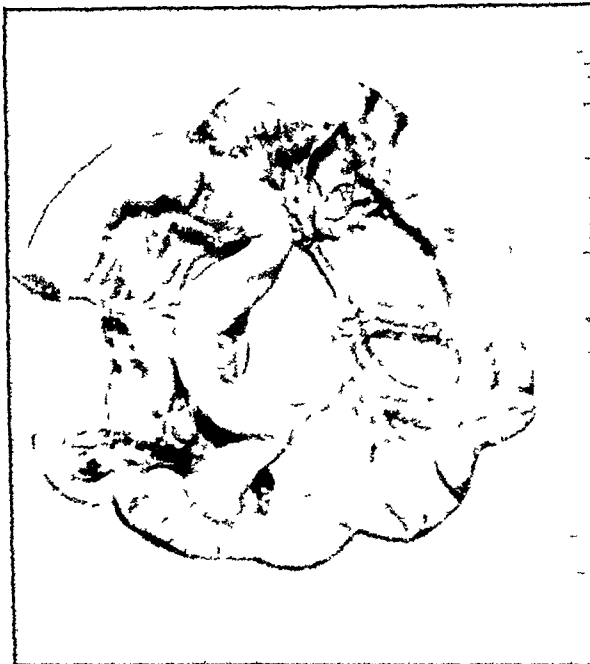
A



B



C



D

FIG 8—Postmortem specimens obtained after two types of "Roux-Y" experiments
 A Specimen, Series I, showing dilatation and hemorrhagic necrosis of the free loop, without perforation B Specimen, Series I, showing dilatation, necrosis and perforation of free loop (Pointer indicates site of perforation) C Specimen, Series I, showing necrosis with perforation at site indicated by pointer D Specimen, Series II Note absence of distention and normal appearance of loop (Animal living and well, sacrificed for autopsy)

and physiologic relationship. Ideally the animals should also be of known age and strain and should be vigorous and free from disease."

The morphologic studies, coupled with the other data here presented, emphasize the great vascular reserve of the jejunum and ileum. It is apparent that there are two principal anastomotic routes, one in the arcuate system, the other within the intestinal wall. It has been generally assumed that the former is the only mechanism which can be uniformly counted upon, in fact, this has been considered so important that it is common surgical teaching that not more than 2 cm. of intestine can be safely denuded of its mesenteric vessels. These studies indicate a much greater degree of importance of the intramural anastomotic system than had previously been supposed, these anastomoses apparently can compensate for rather large losses of mesenteric vessels. It is interesting in this connection to note clinical reports of recovery following traumatic severance of several inches of the mesenteric supply.²⁶ Survival in these cases was attributed to blood supply developed from omentum wrapped about the loops at operation. While such may have taken place, our studies would indicate that actually it was probably the efficiency of the intramural anastomoses which maintained the viability of the intestine. It would be a mistake to consider that our findings justify any radical changes in the technic of intestinal anastomosis for one obviously ought to preserve all of the blood supply possible. Nevertheless, we feel that these findings may afford considerable reassurance when circumstances demand greater dependence upon the intramural anastomoses than we had previously thought compatible with survival.

The deleterious effect of distention upon intestinal revascularization might have been predicted but it proved to be greater than we had anticipated. Operative findings and autopsy specimens have frequently indicated that extreme degrees of distention produce sufficient avascularity to cause pressure necrosis and intestinal perforation. Thus the ability to prevent filling by marked distention was no surprise. The degree of vascular interference caused by moderate degrees of distention, however, was greater than anticipated. This finding emphasizes the need for complete intestinal decompression in all conditions associated with intestinal distention. Further, the results indicate a need for constant decompression wherever the integrity of the intestinal lumen is threatened by injury or operative trauma. Therein may lie the explanation for failure of suture lines thought to be adequate but later giving way due to partial avascularity produced by moderate distention.

Loops with proximal closed ends somewhat similar to those used in "Roux-Y" anastomoses were chosen for study because they provided (1) vascularization from one end instead of two and (2) because they were of sufficient length to permit of moderate distention at the free end. When the closed end was vented into the intestine so that the portion farthest from the source of blood supply would be decompressed, necrosis was less likely to occur. While our primary intent was not that of testing the "Roux-Y" type of anasto-

mosis in regard to the integrity of the blood supply, it must be pointed out that our studies do confirm the concept that anastomoses by use of loops are safer from a vascular standpoint since they have blood supply at both ends. This is especially so if the loops are kept decompressed by means of an entero-enterostomy.

CONCLUSIONS

1 Morphologic and physiologic experiments indicate that there are two principal routes for revascularization in the jejunum and ileum (1) The arcuate system of mesenteric vessels, and (2) the anastomoses within the intestinal wall.

2 So long as the arcuate system remains intact it provides a most efficient compensatory mechanism, but when it fails to function the intramural vessels are probably far more effective than hitherto supposed. These vessels alone appear able to nourish several centimeters of jejunum or ileum.

3 Species differences are great both with respect to the mesenteric pattern and the type of intramural anastomosis. These factors should be carefully considered in the selection of experimental animals for investigations referable to man.

4 Distention in any degree produces definite interference with the efficiency of the intramural anastomotic mechanism of the small intestine.

Dr Gordon H. Scott, Professor of Anatomy, has made many helpful suggestions during the course of these investigations.

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DISCUSSION—DR JACOB FINE, Brookline, Mass I would like to call your attention to an experiment done on dogs several years ago by one of my colleagues and myself, in which we obstructed the venous return of loops of small intestine about ten inches long in the dog, with the finding that in every instance when nothing else was done, death from gangrene and peritonitis occurred within 24 hours or less, but that if an antibiotic were placed in that loop a recovery of viability and a return of function took place almost uniformly Distention was not an important factor in these results

I think it is important to stress the fact that viability of a loop of gut with deficient blood supply is conditioned by local bacterial action as well as by the degree of vascular impairment

HERPES ZOSTER A SURGICAL PROCEDURE FOR THE TREATMENT OF POSTHERPETIC NEURALGIA*

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Numerous studies of material derived from postmortem examination of patients who had manifested clinical features of herpes zoster have shown outstanding pathological lesions in one or more dorsal root ganglia. Associated processes in the spinal cord, the posterior roots, the peripheral nerves, and the dermatomic zone of skin subserved by the implicated ganglion or ganglia have been equally well authenticated. Also there are many recordings concerning the clinical aspect of the disorder. Certainly the available elaborate descriptions of the changing skin eruption during the acute phase of the disease leaves little to be added. In attempting to correlate these clinical and pathological observations, especially the problem of the pathophysiological mechanism that produces postherpetic neuralgia, one finds oneself on less secure ground. It has been implied, and seemingly with quite general acceptance, that the obvious changes in the dorsal root ganglion are in some manner responsible for the alterations in afferent pathways, and hence the pain. Possibly this is true, however, we have made observations that have prompted us to question the validity of this deduction. From an over-all consideration of the subject, we have evolved a therapeutic approach for postherpetic neuralgia different from those previously employed, namely, excision of the involved skin and subcutaneous tissue.

THE CLINICAL PICTURE

There appears to be a general belief that herpes zoster is a disease that affects the aged and debilitated. While it may occur at any age, there are seldom enduring sequelae among those afflicted before the fourth decade of life. There is no available knowledge relative to the portal of entry of the infectious agent, and the early systemic responses—mild fever, general malaise and “muscle ache”—offer no clue as to the manner of invasion. It is only after the appearance of a cutaneous erythema, with scattered small vesicles distributed in a dermatomic fashion, that the clinician becomes certain of the nature of the disease. Concomitant with, or at times just preceding the development of the rash, the patient's attention is attracted to the affected part by an increased sensitivity of the segment of skin that is becoming involved. Shortly after the appearance of the erythematous rash the hypersensitive cutaneous area takes on a burning discomfort which is commonly aggravated even by the pressure of light clothing. Added to this discomfort are intermittent

* Read before the American Surgical Association, St Louis, Mo, April 21, 1949

spells of sharp stabbing pain, sometimes described as extending through the part affected, whereas in other instances the pain tends to follow the surface of the dermatome implicated. During the second week of illness, blebs appear. In mild cases, these are small and separate but with varying degrees of elevation of erythematous skin between them. Only a part of the dermatome, about the size of one's hand, may show the cutaneous lesion. In such cases, if the involvement is thoracic, the blebs may be situated paravertebrally or, less frequently, anteriorly. Under these conditions, even though the remaining portion of the dermatome manifests no visible lesion one may demonstrate by appropriate stimuli that the sensory receptors of the entire segment are altered.

In severe cases, the erythema covers the full extent of the dermatome, the blebs are larger and tend to coalesce, the burning discomfort is continuous, and any movement that changes the tension of the skin of the area precipitates sharp stabs of pain. The patient becomes distraught with the constant day and night discomfort. Medication, regardless of its potency, offers only temporary relief.

In the majority of instances, the erythema begins to recede during the third week. The blebs show crusting and wrinkling, and scattered small open wounds resulting from rupture of some of the blebs may be present. Both the drawing, burning discomfort and the recurring sharp pain become less disturbing. By the fifth to sixth week, the scales of the encrusted blebs have fallen away, leaving bizarre-shaped pink scars. The previously erythematous areas not implicated by the blisters take on a light brownish hue. Gradually the scars retract, thereby producing pocks devoid of pigment. The end result is an irregular-shaped tongue of skin, within the confines of a dermatome, mottled by pigmentation and freckled with pocks lacking in normal pigment. For a time, the area remains mildly "tender" to rubbing, but this slowly subsides and by the end of two or three months the patient has recovered symptomatically. Cutaneous evidence of the disease usually remains for years.

Other patients do not fare so well. The coalescing blebs often rupture if not well protected from external pressure, and a large part of the dermatome becomes covered with a weeping crust. The long continued twisting, burning pain resulting in sleepless nights may lead to an abnormal psychologic state. Patients so afflicted not infrequently speak of suicide as the only way out of their torment. In truth, one who came under our observation was admitted to the hospital following a leap from a third story window, and died shortly thereafter. In some instances, especially in older patients, desquamation and re-formation of crusts over the herpetic area may continue for as long as ten months.

Although the burning and intermittent sharp shooting type of pain may persist for months, or even years, after the acute phase of a relatively mild attack of shingles, this occurs only in exceptional instances. More commonly, the so-called postherpetic neuralgia is encountered in the fifth, sixth or seventh

decade of life, and usually follows a severe attack of zoster. At all events, postherpetic neuralgia is a well established clinical entity that may be a continuation of or, more infrequently, a sequel of herpes zoster. It is with this complication of zoster involving the trunk and extremities that this presentation is chiefly concerned.

In postherpetic neuralgia, the outstanding complaint is variously described by the patients as twisting, burning, drawing, boring, pressing or sharp shooting. The pain is usually limited to the zone of pocked and bronzed skin of a single dermatome. In one case in our experience the sharp stabs of pain were referable to dermatomic segments caudad to the ones bearing the overt scars of the acute attack. By the time the patient comes under the observation of the surgeon, many forms of physical and medicinal therapy have been tried with little if any beneficial effect. Examination discloses the obvious zone of skin involved. As is often observed in patients with long-standing discomfort of a part, the results of detailed sensory examination are not wholly reliable. In some patients with zoster even the slightest superficial pressure is said to cause a burning pain. Since certain alterations in cutaneous sensations have been demonstrated sufficiently often in the same patients, and these changes have been essentially the same from case to case, one can be reasonably sure that they are dependent upon organic changes and should not be attributed to an abnormal psychological trait. By lightly drawing a sharp object over the normal and onto the abnormal skin, the dermatome involved may be delineated. Within this zone, touch is usually blunted or absent. Over the scars touch is not appreciated, whereas the bronzed or relatively normal-appearing skin is hypesthetic. Pin prick as well as excessive degrees of heat and cold, used as stimuli, produce a spreading burning pain. Two-point discrimination seems impaired, however, the application of the points frequently produces a burning sensation, thereby making this interpretation questionable. In all events, the findings resemble those that result from a partial physiologic interruption of a peripheral nerve.

PATHOLOGIC CONSIDERATIONS

The infectious viral nature of the disease is generally assumed. As early as 1861, von Barenprung,² by means of little more than naked-eye postmortem examination, recognized that swelling of a dorsal root ganglion was associated with the cutaneous lesion known to several generations as "zona." On the basis of a most meticulous analysis of postmortem material in 21 cases, Head and Campbell,¹ in 1900, published a classical discourse on the pathological lesions, not only of the skin and dorsal ganglia, but also of the dorsal roots, the spinal cord and peripheral nerves. A host of subsequent reports have amplified their observations.

The inflammatory and degenerative changes in the ganglia, nerve trunks, spinal cord, and skin that characterize the active phase of the disease eventually give way to scarring not dissimilar to that encountered in the end stages of other inflammatory processes. The pathogenesis of the complication known as

postherpetic neuralgia might logically be attributed to these anatomical alterations, but its occurrence in only occasional cases is difficult to explain

Information concerning the late pathological changes in the skin, especially those pertaining to the fate of cutaneous sensory receptors, seems rather incomplete. The surgical procedure herein reported afforded specimens of skin

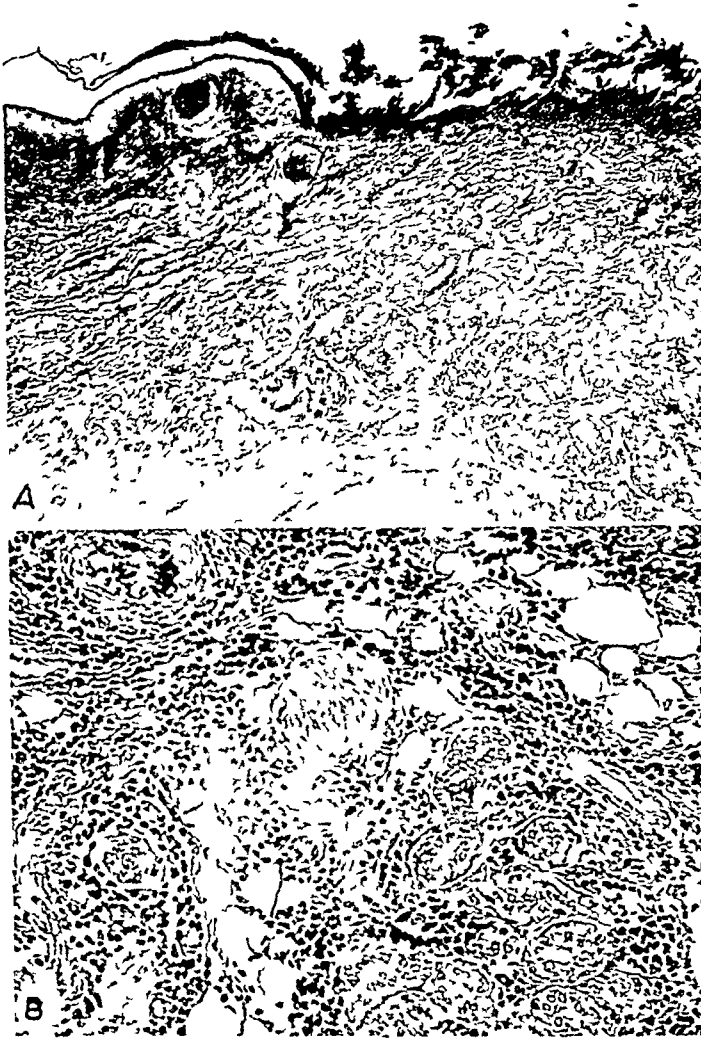


FIG 1—Skin and subcutaneous tissue from an active case of herpes zoster, of 41 days' duration, obtained at autopsy (A) An encrusted ulcer is shown above and to the right. Heavy cellular infiltration involves the entire derma and extends into the subcutaneous area (B) Subcutaneous glands, blood vessels and nerves are shown surrounded by leukocytes which are predominantly plasma cells

from patients suffering from postherpetic neuralgia which were removed after varying intervals following the disappearance of the rash. Other specimens obtained at autopsy supplemented this material.

The early lesions in the skin consist histologically of eruptions characterized by vesicles not unlike those of herpes simplex and herpes progenitalis. These

are acute inflammatory lesions manifesting local hyperemia and exudation of fluid into interstices under and among the deeper epithelial cells, and resulting in the formation of blebs covered by the more superficial layers of cells. The epidermal cells undergo both proliferative and degenerative changes, the most striking of which are the appearance of intranuclear inclusion bodies. Leukocytes, consisting largely of plasma cells, accumulate in large numbers in the underlying derma and, in company with polymorphonuclear leukocytes, make their appearance among the disordered epithelial cells and in the fluid within the vesicles. The latter, whether they rupture or not, become crusted over and the area involved eventually becomes healed by fibrosis with re-epithelialization of the surface. It is the site of the healed vesicular lesion that is represented by a white scar that remains visible for years after the subsidence of the acute process.

In addition to the more obvious superficial lesions, the skin is the seat of varying degrees of diffuse inflammatory infiltration involving all levels of the corium and extending into the subcutaneous tissues. There is a marked tendency for the aggregation of leukocytes in masses about the blood vessels and nerves, and even about the hair follicles, sebaceous and sweat glands. In a patient who had been driven to suicide by 41 days of severe pain of herpes, we found occasional small ulcers with crusted surfaces, each lined by a zone of seminecrotic tissue heavily infiltrated with polymorphonuclear leukocytes (Fig 1A). In the adjacent "live" tissue, the infiltration was predominantly plasma-cellular, but included scattered neurophilic and occasional eosinophilic polymorphonuclear cells (Fig 1B). Numerous focal collections, chiefly of plasma cells, were present in closely-spaced foci within the derma and subcutaneous tissues. Within these lesions many nerves were visible. Occasionally an isolated nerve was seen surrounded by a mantle of plasma cells. Only very few lymphocytes were found in the involved skin in this case. The dorsal root ganglion subserving the implicated dermatome and also the ganglia adjacent and on the opposite side showed heavy infiltration with leukocytes of the same types and in about the same proportions as those found in the skin. These lesions were interpreted as representing a chronic active phase of the inflammatory disease.

Study of the excised skin from a patient in whom the acute manifestations of herpes had subsided about 100 days before, revealed a remarkable degree of persistence of inflammation but, in addition, numerous small densely collagenous scars. The infiltrating cells were composed chiefly of plasma cells, but included a good many lymphocytes. No polymorphonuclear cells were present. The aggregations of cells were more compact than in the case cited above, and there was no diffuse inflammatory infiltration. The scars were occasionally situated deeply within the derma and subcutaneous tissue (Fig 2A). More frequently, they could be followed inward from the surface as wedge-shaped or fusiform scars suggestive of small neuromas (Fig 2B). One dermal lesion located about a blood vessel presented a tubercle-like structure and contained

giant cells of foreign-body type (Fig 3 A) Another focus had become ossified, containing a central cellular island in which giant cells of osteoclastic type were evidently associated with the production of marrow within this focus of metaplastic bone formation (Fig 3B) The lesions in this case were considered to represent an example of severe skin involvement in a stage of the disease in

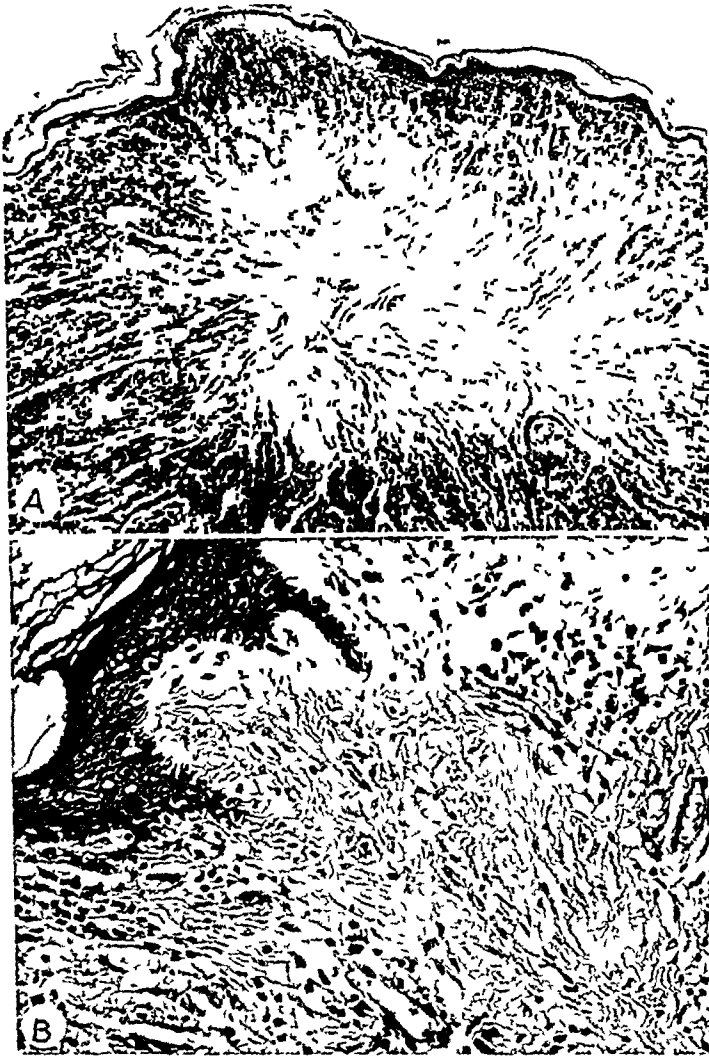


FIG 2—Skin surgically excised for relief of postherpetic neuralgia (A) A deep-seated radial scar with overlying atrophic epidermis (B) A fusiform scar extending inward from the epidermal surface at a site of puckering. Clusters of plasma cells and lymphocytes are still present 100 days after clinical subsidence of the acute phase

which advanced healing and persisting active inflammation of subacute type were simultaneously present. Postherpetic neuralgia had been severe until surgical excision relieved the condition.

Still another type of pathologic picture was presented in skin from a woman who died of myocardial infarction 34 months after the onset of herpes and 32 months following the subsidence of clinical evidence of activity in the involved dermatome. This patient showed inconspicuous widely scattered foci

of cellular infiltration, and the cells were almost entirely small lymphocytes. Only small compact scars were present and were situated chiefly within the derma. This case was classified as representing the end or healed stage of herpes.

In all of the cases studied, atrophy and distortion of the epidermis, with abnormalities of pigmentation, were encountered.

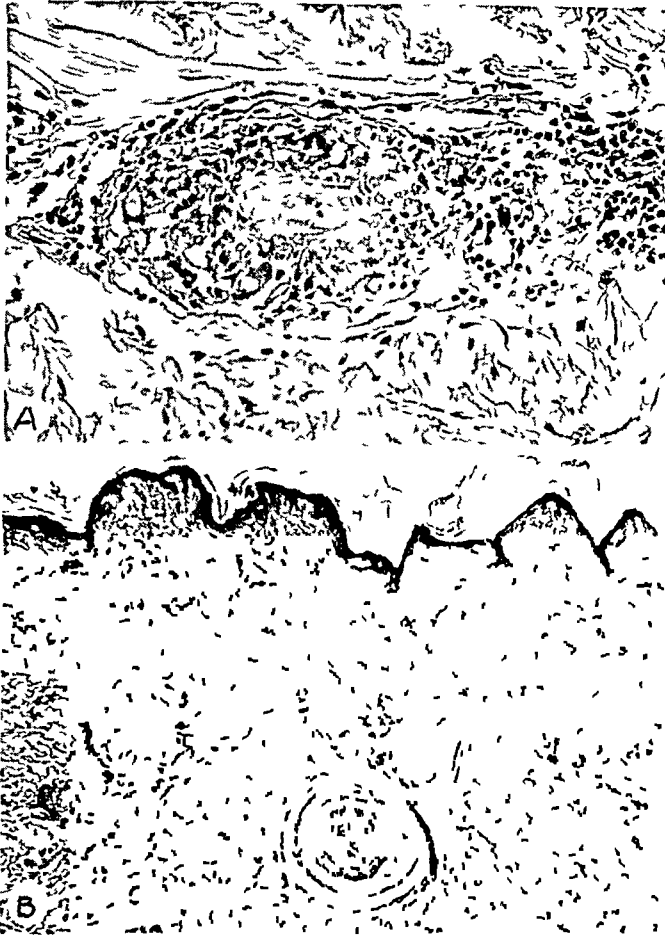


FIG 3—(A) Tubercle-like dermal nodule formed about a blood vessel. Giant cells of foreign-body type are evident. (B) An island of bone interpreted as the result of metaplasia in a scar is situated beneath the atrophic distorted epidermis. Hair follicles and sebaceous glands are absent.

It would seem logical to assume that the implication of nervous structures within inflammatory cutaneous foci in all phases of the disease might be responsible for the persistence of pain and other sensory disturbances encountered in those who suffer from "postherpetic neuralgia."

SURGICAL EXPERIENCES

In view of the debilitation that results from postherpetic neuralgia, and the ineffectiveness of medicinal and physical therapy, including roentgen ray, it

seemed logical to explore further the possibility of surgical help. Many approaches to the problem have been carried out by numerous surgeons, all aimed at interrupting the pain-conducting pathways coursing from the affected parts. Although none of these operations has been entirely successful, many of them have served as useful experiments. The injection of various sclerosing chemicals, alcohol in particular, paravertebrally and into the spinal subarachnoid space has been of no avail, and further consideration of this method of treatment does not seem profitable. There are three surgical procedures—anterolateral cordotomy, dorsal rhizotomy, and sympathetic ganglionectomy—that merit discussion, although their use singly or in combination has not

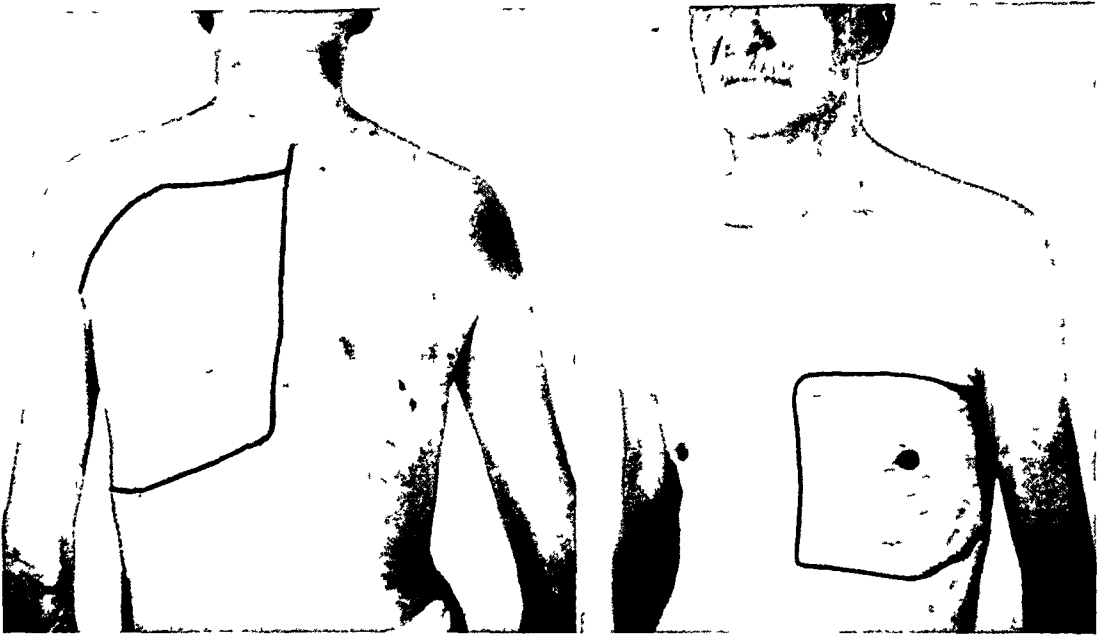


FIG 4—Patient with postherpetic neuralgia treated by anterolateral cordotomy and dorsal rhizotomy. The lines indicate the limits of the anesthetic and analgesic area. Relief of pain was not obtained.

resulted in complete relief of pain. The recitation of an abbreviated case report will suffice to review our experience with two of these three procedures.

A 67-year-old carpenter was admitted to the hospital complaining of burning and, at times, sharp shooting pain around the left thorax at the level of the T-7 and T-8 dermatomic zone. Two years prior to entry there had been a moderately severe attack of shingles, followed by pain described "as if someone was pulling on the skin of the chest with a pair of pliers." Many types of medicinal therapy had been tried, but so far as could be determined no opiates had been used. The left T-7 and T-8 dermatomic areas were mottled with irregularly bronzed skin and widely scattered whitish pocks. The first operation consisted of a right anterolateral cordotomy which effectually abolished appreciation of painful and thermal stimuli from the T-4 level distally on the left side. The loss of these modalities of sensation began at a point well above the upper aspect of the bronzed zone, yet the patient insisted that the pain was unaltered. Pressure over the segment of affected

skin with either a sharp or blunt pointed object precipitated a burning sensation, whereas before operation only the prick of the pin caused this type of pain. Because of the findings it was concluded that depriving the area of all form of cutaneous sensation might relieve him. Accordingly, a dorsal rhizotomy (T-3 through T-9) was performed. After this operation the zone of bronzed, implicated skin occupied about the middle of a completely anesthetic and analgesic area (Fig 4). Pressure with any type of object along the bronzed zone still precipitated a burning type of pain. Moreover, spontaneous pain continued about as before the first operation. Six weeks following entry to the hospital the patient was discharged, complaining possibly more of the thoracic discomfort than when admitted. The neuralgia persisted until his death one year later in another hospital, death following an operation for prostatic hypertrophy with urinary retention.

Comment Not all of our efforts have been so futile, for there are some patients who have had considerable relief following anterolateral cordotomy. Most of them, however, have had some residual discomfort, enough for them to question the worthwhileness of the procedure. Sympathetic ganglionectomy, namely removal of the second through the tenth thoracic ganglia, has been tried in two cases of postherpetic neuralgia of the lower thoracic region. In one, an anterolateral cordotomy failed to effect relief, and the ganglionectomy performed one month later likewise was ineffectual. In the second case sympathetic ganglionectomy failed to influence the neuralgia.

After passing through a period when patients with postherpetic neuralgia were excluded as candidates for any form of surgical therapy, it was decided that there still remained one possible approach that had not been given a trial, that is, excision of the involved skin and subcutaneous tissue. After explaining the experimental nature of the procedure to several patients who seemed appropriate subjects, one of them finally consented to the operation. The following summary indicates the clinical picture of the disease and the operative procedure in this case.

A 70-year-old man had had diabetes mellitus for eight years, and also had had attacks of angina pectoris at irregular intervals for four years. During the early part of January, 1945, there was first noted a band of pinkish-colored skin extending from the axillary region around the right side of the chest to the mid-line posteriorly. There was mild itching and some burning for the first six or seven days of illness. At the end of this time many small blebs began to appear, and within another two weeks the area comprising what was considered right T-7 and T-8 dermatomes was covered with varying-sized blebs. Medicinal measures, including injections of pituitary extract, were given in an attempt to relieve the constant burning pain, but were of little avail. Four roentgen ray treatments (300 r each) were given three days apart without appreciable amelioration of symptoms. By the end of seven weeks from the onset of the illness, the blebs had dried and the scales had exfoliated, leaving a band of bronzed pock-marked skin 7 to 8 cm wide about the chest. In addition to the burning, boring type of pain, there were added periods of sharp shooting pain along the implicated dermatomic zone. Even opiates, which were eventually resorted to, failed to give sufficient respite for sleep. He was admitted to the hospital on June 5, 1945, at which time examination disclosed moderate arterial hypertension, mild cardiac enlargement, and diabetes mellitus. The findings of importance were related to the zone of irregularly bronzed skin somewhat mottled by the typical pocks of healed herpes zoster. The slightest touch of the skin caused the patient to withdraw quickly from the examiner's hand. It could be demonstrated that the shiny skin covering the larger pocks

was hypesthetic, but upon stimulating the involved area a burning pain was precipitated which continued for seconds after withdrawing the stimulus

On June 6, 1945, under novocain anesthesia, a segment of skin 9 to 10 cm wide and 60 cm in length, including all of the bronzed area, was removed. Following complete healing of the wound the patient was discharged from the hospital on the twenty-first postoperative day (Fig 5). All medication was discontinued and he remained comfortable until about the middle of April, 1946, when he noticed that touching a certain spot in the right anterior axillary line just caudad to the surgical scar produced a sharp shooting pain that radiated along the scar into the back. Examination at the time showed that either a pock had been overlooked at the operation or a new one had formed. Touching this single pock precipitated the pain. He was readmitted to the hospital on May 13, 1946, and a relatively small piece of skin including the offending pock was excised. Since the second



FIG 5—Patient for whom a zone of skin, 60 cm in length and 9 to 10 cm in width, was removed. Postherpetic neuralgia was completely relieved.

operation, he has remained comfortable as regards the postherpetic neuralgia, and when examined recently even rubbing the surgical scar produced no discomfort.

Comment The result of this case demonstrated that fairly satisfactory relief of postherpetic neuralgia could be obtained by excision of the involved skin and the underlying subcutaneous tissue. Moreover, this experience seemed to indicate that the cutaneous nerve fibers and/or sensory receptors were a part of the abnormal neural mechanism responsible for the pain.

The second operation was carried out on a 60-year-old man. The bronzed and pock-marked skin was situated in the posterior part of the right T-7 dermatome zone. One could demonstrate cutaneous hypersensitivity through the right half of the T-7 segment, but there was little if any discoloration of the skin anteriorly, and no pock marks were visible there. The drawing, burning pain, with occasional sharp stabs, was located in the area with obvious cutaneous changes. It was planned to perform the operation in two stages. The posterior half of the right T-7 zone, including the pock area,

was removed under local anesthesia. Generous undermining of skin permitted closure. Primary healing ensued.

Comment The relief of pain was so complete that the patient refused to have the anterior segment of skin excised. When last seen three years after operation he had remained free of pain.

The third patient subjected to the operation, a man age 64, presented a clinical picture very similar to the first, and the treatment was the same except that the excision was performed in two stages. In this case, the burning pain was relieved but there has persisted an occasional sharp stab of pain "through the chest." The result, two years after operation, was considered moderately satisfactory.

Comment Both the second and third patients were rugged, stoical individuals who had performed manual work all their lives. It seems possible that the third man had more pain than he would admit, sensing our hope that the result was satisfactory.

The experience with the fourth patient deserves more elaborate presentation than that accorded the second and third.

A 77-year-old man was admitted to the hospital on August 18, 1947, complaining of burning pain in the lower part of the back, upper hip, and around the lower abdomen on the right side. Occurring at irregular intervals, especially when these areas were touched, there was sharp stabbing pain of a radicular distribution. There had been an attack of shingles approximately one year before he entered the hospital, and according to the story it had been rather severe and had lasted for three months. Examination disclosed the right T-10 and T-11 dermatomes to be mottled and extensively scarred, especially paravertebrally and over the right lower abdomen. On September 8, 1947, a segment of skin comprising the anterior half of the involved segment was excised. In order to close the defect, the skin was generously undermined down over the groin and regionally over the upper abdomen. Closure without undue tension was obtained, and this with the right lower extremity in full extension. Immediately postoperatively, the patient assumed a position of flexion of the right thigh to relieve the tension on the operative area. Considerable serosanguineous fluid accumulated in the free space created by the undermining procedure, although the area had been drained for 48 hours.

At the end of a week, the medial aspect of the wound opened, and discharge from this site continued for 3 weeks, leaving an indolent granulating area. After he was out of bed he walked in a stooped attitude and was not very co-operative in our attempts to have him "stretch" the skin of the right lower abdomen and groin. On November 27, 1947, the posterior half of the area of pock-marked skin was excised. The edges of this wound also partly separated, and the subsequent skin grafting to aid in epithelialization was not effective. Finally, after a rather prolonged period of treatment, the patient was discharged from the hospital. During the following year he was observed from time to time. There were so many complaints, many of which were not seemingly referable to the area under consideration, that it was difficult to evaluate them. Apparently the burning that was present prior to operation had disappeared. Roughing the affected part was said to produce pin and needle sensations. At irregular periods, there were recurring sharp stabbing pains in the region of the scar of the lower back and also in both lower extremities.

Comment The difficulties, mostly the result of technical omissions in an elderly patient, have been recorded since it is obvious that many of them should have been avoided. The area deprived of skin and subcutaneous tissues should have been covered with a primary skin graft rather than closing the

wound after extensive regional undermining. In very elderly patients any discomfort is poorly tolerated, consequently if the situation producing the original complaint cannot be corrected without sequelae the advisability for any surgical therapy is questionable.

DISCUSSION

The mechanism for the production of postherpetic pain is not known. It has been reasonably well established that afferent impulses initiated by stimuli within a peripheral part do not traverse the ganglion cells of the dorsal root ganglia. This does not exclude the possibility that chronic pathological changes in a ganglion may in some manner lower the threshold of excitation in the cutaneous receptors. On the other hand, these obvious changes in a dorsal root ganglion as seen in examples of zoster may not be directly concerned in the production of postherpetic neuralgia, but merely represent the results of an active inflammatory process in this anatomical structure. It therefore seems proper to consider each anatomical component of the peripheral neural mechanism that may be involved in postherpetic neuralgia. A comparison of the findings in postherpetic neuralgia with those of other pathological states may somewhat elucidate the problem.

Skin lesions produced by accidental burns with various chemicals, when completely healed, may present an appearance very similar to the superficial residual of herpes zoster. Touch is not appreciated normally in the focally scarred areas, a finding somewhat comparable to that in zoster. The prick of a pin is also blunted in the scars in both conditions, but produces the spreading burning pain only in zoster. Moreover, the patients with scars from burns have not complained of the sharp stabbing pain so characteristic of postherpetic neuralgia. It therefore seems unlikely that the pathological process in the skin in zoster is the sole change that can be logically charged with the causation of postherpetic neuralgia.

The cutaneous sensory findings in zoster are almost identical with those characteristic of a "regenerating peripheral nerve." After division and suturing of a peripheral nerve in an anatomical position there follows, after variable periods, a return of appreciation of pin prick and differentiation of certain degrees of heat and cold. During this early phase of recovery touch is not appreciated and two-point discrimination is grossly altered. One may readily outline the denervated zone of skin by drawing a sharp object over the normal and onto the abnormal skin, as in zoster. Also, as in zoster pin prick and excessive degrees of heat and cold when used as stimuli produce a spreading burning sensation, and roughing the part is also painful. In some patients there are, as well, sharp stabs of pain into the affected part, as described in postherpetic neuralgia. Therefore one cannot dismiss the possibility that the infection in some cases of zoster may produce a partial permanent interruption in peripheral nerves that may account for the neuralgia.

Primary lesions limited to the dorsal spinal roots are exceedingly rare. In two cases we have observed segmentally distributed cutaneous vesicles follow-

ing the spinal subarachnoid injection of alcohol. The promptness of the appearance of the blebs after injection made it appear that the effect of the alcohol on the spinal roots may have been responsible for their appearance. More likely, some of the alcohol penetrated the dorsal ganglion at the lateral extremity of the subarachnoid sleeve. The absence of vesicular eruptions following damage of dorsal roots by tumors as well as by surgical procedures of one sort or another makes it seem unlikely that a partial physiological interruption of these filaments by the inflammatory process incident to an acute attack of zoster could, at a later period, account for postherpetic pain. Finally, the segmental nature of postherpetic neuralgia would tend to exclude a lesion within the spinal cord as the causative factor.

Pain localized to a surface area, but due to a more central lesion, may be temporarily relieved by infiltrating the painful zone with an analgesic such as novocain. In some patients with this type of "reference pain," repeated infiltrations will eventually produce complete cessation of the discomfort. This therapeutic procedure is frequently used empirically in the treatment of pain of indeterminate origin, but has a sound pathophysiological basis. It has been used effectively during the acute phase in some cases of herpes zoster. Carrying the principle a step further, Dr. M. Frank Turney, the associate of one of us, two months ago undermined a large area of skin in a case of postherpetic neuralgia. In this patient the implicated skin was so situated that total excision did not seem feasible. Complete relief from pain followed the procedure. However, it is too soon after the operation to make an estimate regarding the ultimate outcome.

From our limited experience, total excision of the skin and subcutaneous tissue of the implicated dermatome offers a better chance of relief than any other method that we have employed. It would seem that the abnormal neural mechanism may be effectively altered by the excision of only a part of the involved dermatome, as was done in the second case of this series. On the other hand, in the first case, a single pock inadvertently left behind at the first operation was sufficient to preserve the abnormal mechanism. It is evident that total excision should not be carried out in some cases, particularly in patients with neuralgia of a part of the head or neck. It has been planned to denervate totally the area supplied by the first division of the fifth cranial nerve in ophthalmic neuralgia following zoster. A large flap of scalp and forehead could be outlined and reflected with the pedicle in the temporal region. Some weeks later, following the establishment of circulation, the pedicle could be sectioned. Various technical procedures may be devised to denervate the segment of skin involved, the best method probably being wide excision of the dermatome implicated.

SUMMARY AND CONCLUSIONS

1. Postherpetic neuralgia, an infrequent but distressing complication of herpes zoster, has been treated in the past by numerous medicinal and surgical measures, but usually to little avail.

2 After consideration of the resemblance of the sensory disturbances in this condition to those of other disorders characterized by a lowered threshold of the skin for various sensory stimuli, it was decided to excise experimentally all or portions of the implicated dermatome in a typical case of postherpetic neuralgia. The result achieved was so highly satisfactory that the procedure has been employed in other cases.

3 The four cases in which involved skin and subcutaneous tissue was excised have been reported in brief. The results were considered excellent in two, moderately satisfactory in the third, and unsatisfactory in the fourth case.

4 Pathological studies of skin excised at operation, as well as skin and other tissues obtained at autopsy from patients with herpes zoster but not subjected to "dermatomectomy," have been briefly recorded. The scarring and persistent inflammatory infiltration noted would appear to be competent contributing factors in the production of the pathological neural mechanism responsible for postherpetic neuralgia. The fact that not all victims of herpes zoster suffer from this complication poses a problem that remains obscure.

5 Proper evaluation of the reported surgical method of treatment for postherpetic neuralgia, and possible modifications of the procedure must await further trial.

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DISCUSSION—DR. BRONSON S. RAY, New York, N. Y. I can add very little to this discussion, but I should like to say that Dr. Browder's paper provides a much-needed fresh approach to an old and very troublesome problem.

In my experience, too, cordotomy and rhizotomy, and even lobotomy, while sometimes providing improvement, on the whole are disappointing in results. It is common and also somewhat paradoxical to find that local agents in the painful area, such as infiltration with procaine and spraying with ethyl chloride, will abolish the pain temporarily.

We have had one experience with the operation after it had been suggested by Dr. Browder. This was a woman 60 years of age, with chronic pain in a scarred band three or four inches in diameter running around the midchest on the right side. A two-stage excision necessitating a skin graft in part of the area was performed.

Whether due to incomplete excision, which is one definite source of failure, it seems to me, or the mental shortcomings of this particular patient, the result was only partially successful, but I am fully prepared to believe that the operation Dr. Browder proposes should provide success in carefully selected cases.

DR. FREDRICK E. KREDFL (Charleston, S. C.) So as not to make this thing seem too perfect, Dr. Browder asked me also to show a case of rather incomplete success.

(Slide) This slide shows a person who had postherpetic neuralgia for six years. Blocks and intercostal nerve section did not relieve his extreme hypersensitivity. A wide

excision of skin was done from midline to midline on the right side well beyond the apparent area of hypersensitivity by testing. This gave him temporary relief, but a year and a half later there was full recurrence, and a second very wide excision was again done. Posteriorly, it was necessary to graft part of the area, as you see here.

An interesting fact is that these grafts, now a year and a half old, have shown no recovery of sensation, since they lie in a denervated field.

(Slide) On the anterior side it was not necessary to graft, but he still has some residual hypersensitivity and burning pain below the incision, and probably will require a third skin excision to complete the relief.

We have had two other cases that have had an incomplete result probably because not enough skin was removed.

DR GILBERT HORRAN (Boston, Mass.) I just want to say that I think it is a very definite contribution which Dr Browder has made to our conquest of pain, and just one word in elaboration of what Dr Ray was saying about local infiltrations.

We have had three patients in whom local procaine injections over a fairly wide area, both in the trunk and one in the scalp, have given not temporary relief in the sense of a few days or a week or two, but relief that has lasted for six months or more. These people have come back at the end of that time for another injection. Some of them have come back many times.

In regard to these methods, I think Dr Livingston could elaborate still further because he has had more experience with it than I have had. It is a very satisfactory method when it works.

DR MIMS GAGE, New Orleans, La. I will probably be out of order in what I have to say after congratulating the essayists on their excellent presentation, which will be of great help to us in treating intractable post-herpetic pain.

I would like to mention a method of treatment of the acute phase (which you probably won't believe) which will cure the disease and prevent undesirable sequelae. This consists in the intravenous administration of neoparsphenamine. One, two or three injections may be necessary. We usually give 0.3 Gm and repeat this on the third or fourth day. This results in relief of pain and drying up of the lesions in 36 to 48 hours.

A friend of mine, Dr Emile Block of New Orleans, has obtained relief of pain and cure in all 25 of his patients with herpes zoster treated by this method. He has used as much as 0.6 Gm but usually gives 0.4 Gm. The results in his cases as well as in mine have been dramatic.

I suggest that you try this form of treatment in your next case. Of course, all the precautions necessary in the use of neoparsphenamine must be observed.

DR JEFFERSON BROWDER (Brooklyn, N. Y.) I wish to thank the discussers. Of necessity this is a preliminary report.

In addition to the four patients who have been subjected to the operation mentioned here, there are six others I know of, three of them seemingly successfully operated on, one with a partial relief, and two failures. As stated, the operation is not considered a cure-all for post-herpetic neuralgia.

CLINICAL AND EXPERIMENTAL STUDIES
OF FLUORESCEIN DYES
WITH SPECIAL REFERENCE TO THEIR USE FOR THE DIAG-
NOSIS OF CENTRAL NERVOUS SYSTEM TUMORS*

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IN THE PAST, many investigators have recorded the use of dyestuffs to delineate malignant tissues with varying success. In most instances, it was found that the dye particles accumulated either in macrophage type cells of the tumor struma or in necrotic areas where the blood supply to the tumor had broken down. In no instance has an appreciable concentration of dye been demonstrated in intact viable tumor cells. This subject has been reviewed elsewhere.⁵

Sodium fluorescein has been injected into patients subjected to laparotomy with the hope that it might accentuate differences in the appearance of normal and malignant tissues. Approximately one gram of the dye (20 per cent aqueous solution) was injected intravenously four hours before the scheduled exploration of patients suspected of harboring an abdominal malignancy. If the injection rate was slow, no untold reaction occurred, rapid injection of the dye resulted in several cases of transient nausea and vomiting. It is well to warn the patient that his skin may be yellow for several days. Although staining of the skin usually disappeared in 24 hours, patients with liver insufficiency remained colored for longer periods of time.

Examination at time of operation was carried out under the ultraviolet light emitted by a CH-4 mercury vapor lamp equipped with a Wood's filter. In addition to the inspection of the tumors in situ, further study was made of sections of the removed specimens. A summary of these cases appears in Table I.

It was early noted that there was no specificity of the dye for tumor tissue but that inflammatory and cystic areas also fluoresced. The most consistent results were obtained with mucinous type carcinomas. In several instances lymph nodes involved by the carcinoma as well as the primary tumor exhibited a marked fluorescence. As noted elsewhere,⁷ carcinomatous peritoneal implants usually fluoresced in contrast to the surrounding peritoneum. Although many interesting phenomena were encountered, the technic per se was not of any practical value.

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The fluorescein technic was extended to include tumors of the central nervous system. In contrast to the lack of affinity of general body malignancies for fluorescein, brain tumors almost invariably showed definite fluorescence when viewed in ultraviolet light.⁸

This technic has been of definite clinical value in the localization and diagnosis of subcortical lesions. Briefly, biopsy material is obtained by aspiration through brain needles inserted into the suspected area. When examined under ultraviolet light, neoplastic tissue fluoresces a bright yellow. Normal cortical material retains a faint yellow-green fluorescence while normal white matter appears blue-white. Edematous tissue which often surrounds brain tumors fluoresces more than normal brain but much less than the tumor itself. In those instances in which the tumor tissue is not aspirated but the biopsy material is fluorescent (edematous) further probing of the same area will usually reveal the tumor. On the other hand, if the brain needle is introduced a second time, to one side, and the material aspirated is less fluorescent, the surgeon will know that he is probing further away from the tumor site.

TABLE I—*Summary of the Degree of Fluorescence Noted in Tumors Other Than Those of the Central Nervous System*

	No. Cases	Excellent	Good	Poor	Failure
Carcinoma of stomach	36	3	14	14	5
Lymphosarcoma of stomach	1			1	
Squamous cell carcinoma of the esophagus	2		1	1	
Carcinoma of the colon	15		2	13	
	—	—	—	—	—
Total	54	3	17	29	5

This method of examination is simple and can be carried out in the operating room itself. The biopsy specimen is collected on a gauze square and handed to the room nurse who, in turn, holds it under the ultraviolet lamp. Thus the surgeon can turn, examine the tissue, and confirm the presence or absence of fluorescence without moving from his operating position. It has not been found necessary to darken the room in order to examine the tissue adequately.

The technic is of further value in that if only small segments of the aspirated material fluoresce, these pieces can be removed separately for section or smear by the pathologist and thus afford him a better chance of establishing a definite diagnosis.

In general, the degree of fluorescence was correlated with the grade of malignancy. Acoustic neuromas and slow-growing astrocytomas took up the least amount of dye, while astroblastoma and glioblastomas appeared to fluoresce the most. Necrotic tumor material failed to take up the dye. Meningioma differed widely as regards fluorescence. While some exhibited only slight fluorescence, others were a brilliant yellow. Metastatic tumors were observed to exhibit a definite fluorescence in every case. In addition, spinal

cord tumors were also found to take up appreciable amounts of the dye in contrast to the surrounding normal nervous tissue

In several cases, after the tumor tissue was believed to be completely removed, residual remnants of the tumor were disclosed by examining the residual cavity directly under ultraviolet light

A summary of 141 consecutive cases in which the fluorescein technic was used and in which a biopsy was obtained is presented in Table II

Many other fluorescent and highly colored dyes have been tested on mice with experimentally induced brain tumors. The majority were rejected because of their toxicity, lack of solubility, or instability. Of the several dyes given clinical trial, all were discarded because of their tendency to color deeply the patient's skin

TABLE II—*Diagnosis of Central Nervous System Tumors with Sodium Fluorescein*

Diagnosis	Fluorescence	Cases
Tumor present	+	105
Tumor present	—	7
Tumor absent	+	2
Tumor absent	—	27
Total cases		141

Attempts have been made to combine fluorescein and similar dyes with several of the heavier elements in the hope of rendering brain tumors radio-opaque to the ordinary roentgenologic examination. To date, no success has been obtained in this particular project. One compound studied, tetraiodophthalic fluorescein, proved useful for intravenous cholecystography¹¹. Other derivatives were found to be too toxic, insoluble, unstable, or highly colored. At present, additional radio-opaque compounds possessing chemical characteristics consistent with the theory of the blood-brain-barrier are being synthesized.

The unsuccessful attempt to synthesize radio-opaque dyes which would aid in the localization of brain tumors prompted efforts to tag fluorescein with radioactive elements. For this purpose, I_{131} is eminently suited, since it has the requisites of relatively rapid decay (half life of eight days), and it emits a penetrating gamma ray (0.367 M E V) which can be detected at a distance. The synthesis of radioactive diiodofluorescein and the initial studies have been previously reported^{6, 10}.

At present, the following technic is being employed. Radioactive diiodofluorescein containing 1 M C of I_{131} is injected intravenously. One-half to four hours later, the activity over symmetrical areas of the head are measured by a specially shielded Geiger-Mueller counter.

The counting rates for each area per unit time can then be compared for localization of the tumor. Care must be exercised that areas over the longitudinal sinus, for example, are not included, since high counts result from the

radioactive dye still present in the blood. In every case, the radioactive localization tests have been done without knowledge of the patient's history or physical findings. The results of these tests have been evaluated independently by members of the neurosurgical staff. The summary (Table III) includes only those patients in whom a lesion was later demonstrated to be present or proved to be absent by operation, ventriculogram, or angiogram.

It should be remembered that among those patients who were later proved to have a tumor, but in whom no tumor was localized by the radioactive dye technic, several had tumors too small (mainly cerebellar tumors), or of such a type (acoustic neuroma) as to contain less than the minimum amount of dye known to be necessary for detection. Other tumors that were not localized were usually found to be deeply situated. The easiest tumors to localize were those situated close to the cortex, malignant glial tumors, and those tumors accompanied by an appreciable amount of edema.

TABLE III—*Localization of Intracranial Lesions with Radioactive Diiodofluorescein*

Tumors correctly localized	22
No tumor localized none demonstrated by angiogram, ventriculogram, or craniotomy	21
Correct localization (but vascular or demyelination rather than tumor)	4
Close to but not exact localization	3
Located as to hemisphere only	1
Tumor present but not located	20
Tumor localized but not found at operation, ventriculogram, or angiogram	2
Incorrectly localized	2
Abscess not localized	1
Cholesteatoma not localized	1
Total	77

In order to study this technic more completely, tracer doses of radioactive diiodofluorescein were injected preoperatively, and biopsies taken of tumor and adjacent normal brain tissue at operation. Equal samples were then measured for their radioactivity. The activity found in human brain tumors ranged from 1/64 to 29 times that of adjacent normal brain.

In general, the highest ratios of activity were found in the more malignant tumors (glioblastoma). Some ratios were probably low because of difficulties in obtaining satisfactory "normal" brain tissue for comparison. For example, there is reason to believe that traumatized tissue or tissue momentarily deprived of its blood supply takes up an appreciable amount of dye. In other instances, a considerable time elapsed between obtaining the normal brain biopsy and the exposure of the tumor and the subsequent removal of a portion for measurement.

For further evaluation of the physical limitations of the radioactive dye technic, measurements were made of a human calvarium containing phantom tumors.⁶ It was concluded that if the concentration of the dye in the brain tumor was twice that of the surrounding tissue, the minimal volume of a tumor that could be detected would be about 40 cc. If greater concentration ratios were present, smaller tumors could be detected.

To expedite the screening of various compounds for their usefulness as diagnostic agents, possible chemotherapeutic effects, and for radiation levels, brain tumors were induced in several strains of inbred mice. The technic employed utilized methylcholanthrene in a manner similar to that of Seligman and Shear¹² and Zimmerman and Arnold¹¹. Since these tumors were induced in inbred mice, subsequent subcutaneous transplants could be carried out with facility. Several glial tumors have been carried for 17 transplant generations.

DISCUSSION

There is no complete explanation at the present time for the increased concentration of fluorescein dyes in brain tumors. That it is not due to a greater vascularity of the tumor is obvious from the fact that maximal fluorescence does not occur immediately after injection of the dye but gradually increases in intensity from one-half to four hours. It has also been demonstrated that tumors with the greatest blood supply (angiomas) are not very fluorescent, and, in fact, have resulted in two diagnostic errors.

Although the so-called blood-brain-barrier undoubtedly is partly responsible for the differential concentration of dye in brain tumors, that it is not wholly so is substantiated by the fact that some gastrointestinal tumors show a similar differential staining. Recent studies (unpublished) would seem to indicate that there is, perhaps, a specific affinity of tumor cells for the dye.

Since the experiments of Goldmann,⁴ the theory of the blood-brain-barrier has occupied the attention of many investigators. Broman^{2, 3} reported that the barrier exists in the intima of the blood vessels in the central nervous system. In experimental animals he was able to damage the barrier by injecting noxious substances into the carotid artery but not by applying them directly to the pia. He also found that the function of the blood-brain-barrier was impaired or absent in brain tumors, encephalomalacia, edema, abscesses, and multiple sclerosis. With this in mind, it is not surprising that we have found a slight fluorescence in areas of edema, and that the more edematous areas contain a greater amount of dye.

In this regard, it would seem that fluorescein and radioactive diiodofluorescein could be expected to be useful tools for further exploration of other diseases of the central nervous system, such as amyotrophic lateral sclerosis,¹ epilepsy, and other convulsive disorders. Fluorescein dyes are excellent for these purposes, since, (1) they are acid chromagen dyes and therefore should not penetrate the normal blood-brain-barrier, and (2) they can be detected and quantitated in extremely small amounts, either by fluoremetry, or by tagging them with radioactive isotopes.

The clinical use of other acid chromagen dyes such as Disulphine Blue has been disappointing. Sufficient amounts of dye to produce sharp color differences between neoplastic and normal brain tissue, when viewed in ordinary light, also deeply stain the patient's skin. This circumstance has proved

* Imperial Chemical (Pharmaceuticals) Ltd, Manchester, England

frightening to the patient, confusing to the anesthetist, and could result in serious medical-legal problems

It is hoped that some of these compounds can be used clinically by tagging them with radioactive isotopes. By this method, very dilute solutions can be utilized

SUMMARY

Sodium fluorescein has been shown to concentrate in an unpredictable manner in many tumors. The most consistent results were obtained in mucinous adenocarcinomas of the gastrointestinal tract and carcinomatous peritoneal implants.

In contrast, tumors of the central nervous system concentrate the dye in a consistent and predictable manner. The use of sodium fluorescein as an aid in the localization of brain tumors at operation is a simple and accurate technic which utilizes no special apparatus except a mercury vapor lamp.

Attempts to use radio-opaque dyes to outline brain tumors have not been successful. The clinical value of the radioactive dye method for the detection of brain tumors preoperatively cannot be evaluated completely at the present time. Better equipment, more sensitive Geiger-Mueller tubes, and other improved methods for detecting radiation should increase the accuracy and consistency of this method.

Mention has been made of the advantages of using fluorescein and radioactive dyes to explore further the role played by the blood-brain-barrier in other diseases of the central nervous system.

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THE CLINICAL USE OF RADIOACTIVE PHOSPHORUS IN THE SURGERY OF BRAIN TUMORS*

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IT HAS LONG BEEN RECOGNIZED that there is need for some physical or chemical method which will permit the accurate localization and demarcation of cerebral gliomas. Since the precise localization of subjacent cerebral tumors is often obscure even after exposure of the overlying cortex, and since an infiltrating glioma is frequently difficult to distinguish from adjacent normal brain, a number of efforts have been made to obtain such differentiation by the introduction of a substance into the circulating blood in the hope that it would preferentially localize in the tumor. Sorsby, Wright, and Elkeles¹ reported such attempts in 1942 employing a 10 per cent solution of kiton green. They were able to stain granulomatous tissue and traumatized brain but did not secure useful staining of gliomas. The same unsatisfactory results were obtained with Evans blue (T-1824) in small doses, this agent had the additional disadvantage in large doses of concentrating in subcutaneous connective tissue.² Moore and his collaborators³ first succeeded in staining gliomas with a vital dye, fluorescein. They found that fluorescence of tumor tissue under ultraviolet illumination was obtained and that little or no fluorescence was demonstrated in adjacent normal tissue. Moore⁴ was able also, by ingeniously tagging fluorescein with radioactive iodine, I¹³¹, to obtain a method which was useful in the approximate localization of cerebral tumors externally through the skull.

This investigation has concerned itself with an attempt to discover a readily detectable substance which would demonstrate a higher concentration in cerebral tumor tissue, particularly in the gliomas, than in normal brain, in order that it might be employed for precise localization and demarcation of brain tumors at operation. It was decided to seek a radioactive material which, either because of a more rapid metabolic turnover in the lesion than in normal brain, or simply by virtue of a local breakdown in the blood-brain

* Dr Selverstone was a Senior Fellow in Neurology, The National Research Council during a part of this study. The United States Atomic Energy Commission gave the radioactive phosphorus used in this investigation. The work reported here has been supported in part by an Institutional Grant of the American Cancer Society, the Office of Naval Research, and the National Foundation for Infantile Paralysis. This paper was read before the American Surgical Association, St. Louis, Mo., April 22, 1949.

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barrier, would exhibit an increased concentration in cerebral tumor tissue. Certain theoretical considerations limited the search for this substance.

1 The most important requirement is that the substance must preferentially localize in the lesion to such a degree that an easily measurable difference in radioactivity can be demonstrated between the lesion and the surrounding brain.

2 It is necessary that the chemical toxicity of the substance be low in order to permit its use in adequate quantity.

3 The half-life of such a radioactive material must be sufficiently long to permit reasonable convenience in obtaining and storing it, and short enough to minimize the exposure of the patient to ionizing radiation.

4 In order to obtain precise localization it is important that the substance be a beta emitter with sufficiently soft radiation to be effectively absorbed within a relatively narrow area about the tumor. A gamma emitter such as Br^{82} , Na^{24} or I^{131} would thus be unsuitable because of the extensive range of such radiation.

It was early suspected that the phosphate ion $\text{HPO}_4 \rightleftharpoons \text{H}_2\text{PO}_4$ might be a useful substance, since there was reason to believe that in all three of the major fractions ordinarily studied in tissue chemistry the phosphate ion might preferentially concentrate in tumor tissue when compared with normal brain. The importance of the phosphate ion as the major intracellular anion of the body would suggest a more rapid turnover of the substance in the *inorganic fraction* of a rapidly metabolizing tumor than in the relatively static normal brain tissue. The work of Changus, Chaikoff and Ruben⁵ has demonstrated that the turnover of P^{32} in the *lipid fraction* of brain is low as compared with other organs. Since there was no reason to believe that this property would also be exhibited by gliomas, it was hoped that this fraction also might show an increased concentration of P^{32} . It was considered possible also that the high concentration of proliferating cell nuclei in tumor tissue as compared with normal brain might be reflected in an increased uptake of P^{32} in the nucleoproteins of the *protein fraction*.

In addition to these metabolic considerations, the phosphate ion was considered a likely material in view of the work of Friedemann⁶ who has shown that the effectiveness of the blood-brain barrier is greater in the case of negatively charged than of other particles. If a local defect of the barrier exists in the tumor, we might thus be provided with a mechanism for differential uptake.

The extensive employment of P^{32} in large therapeutic doses in polycythemia vera and in certain of the chronic leukemias⁷ without dangerous toxicity suggested that it could be used with relative safety in this study.

The half-life of P^{32} , 14.3 days, is a convenient one and its emission consists of pure negative beta radiation with a maximum energy of 1.69 Mev. This energy level has been shown to permit a maximum penetration in brain tissue (assuming a density of 1.0) of approximately 7 mm.⁸

A preliminary study⁹ demonstrated to our satisfaction that in glioblastoma multiforme and in astrocytoma, as well as in certain nongliomatous intracranial tumors, a very satisfactory difference in the uptake of radioactive phosphorus, P^{32} , was present when tumor was compared with normal brain. The patients of this early group were studied employing doses of from 8 to 3.8 millicuries of radioactive phosphorus, P^{32} , as buffered phosphate ion. The specimens of tumor and of normal brain were obtained at operation or at autopsy. An "activity ratio," representing for equal weights

$$\frac{\text{radioactivity of tumor}}{\text{radioactivity of white matter}}$$

was found to vary from 5.3 to 11.0. This ratio appeared to be eminently satisfactory for purposes of localization, and accordingly studies were next directed toward the development of a suitable miniature Geiger-Mueller counter which could be employed as a probe for the accurate localization and demarcation of these tumors.

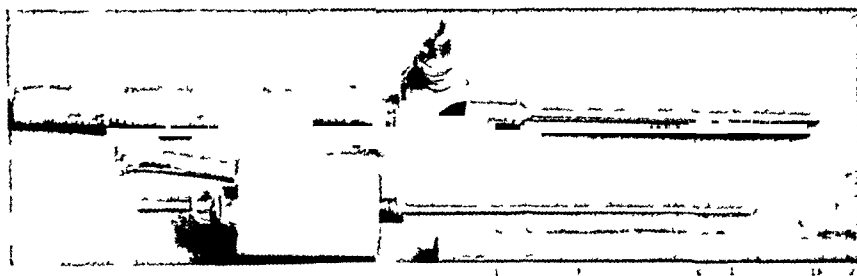


FIG. 1.—The 3 mm and 2 mm probe Geiger-Mueller counters, employed in localization and demarcation of cerebral tumors.

In order that a Geiger-Mueller counter might be used as a probe within the brain, it was considered desirable that the dimensions of the portion entering the brain approximate those of the ventricular needles customarily employed for this purpose. Since it is important that the depth of the neoplasm as well as its surface projection be determined, it was considered necessary that the sensitive volume of the counter be located near the tip. When this research was undertaken, no such counter was available. It was essential to find a suitable combination of noble and quench gases and to determine optimum pressures for counters of these dimensions, as well as to develop a technic of construction. The first counters used at operation were 5 mm and 3 mm in diameter and were filled with an argon-ether mixture.¹⁰ For several months 3 mm counters filled with argon-ethyl acetate have given good service. More recently, 2 mm counters of this type have been used. The probing portion of such a counter is, therefore, of diameter comparable to that of a ventricular needle.

The counters are sterilized by immersion in a formalin germicide for 20 minutes or more. The cable connecting the counter to the associated apparatus is autoclaved. The preamplifier and scaling circuit remain outside the sterile field.

In a brief preliminary report¹¹ our use of the earlier argon-ether counters in the location of 14 deep brain tumors was noted. This work has been amplified, and it is now possible to report 33 cases in which the method has been employed chiefly for localization, but also for demarcation of tumors from surrounding brain.

METHOD

The patient is given a single intravenous injection of buffered radioactive phosphate ion of from .95 to 4.2 millicuries preferably at least 24 hours before operation, but time intervals of from 1.8 to 186.8 hours have been employed.

TABLE I—*Localization of 14 Glioblastomas by Means of the Probe Counter, with Attempt at Demarcation for Total Extirpation in Six Cases*

Case	Time in Hours After Injection of P ³²	Corrected Counts per Minute		Ratio of Counts	Useful for Demarcation of Tumor
		Tumor	Brain		
H F	3.3	2238	99	22.6	—
E P	13.4	684	55	12.4	—
G H	17.0	1982	27	73.4	—
A G	19.3	12668	2168	5.8	+
J D	21.0	2128	222	9.6	—
F F	21.1	2125	219	9.7	+
A H	22.7	1134	35	32.4	+
A P	25.3	30077	828	36.3	+
A C	25.6	2946	482	6.1	—
W B	26.8	8829	349	25.3	—
A A	26.9	4539	783	5.8	+
A B	43.6	13032	1207	10.8	—
D C	46.5	2885	390	7.4	+
M G	186.8	2034	250	8.1	—

No other preparation of the patient is necessary. The appropriate standard methods of approximate brain tumor localization are fully utilized, and the location of the exposure to be made of cerebral or cerebellar cortex is determined by neurologic examination and by electroencephalographic and ventriculographic data.

A "control area" is first chosen, usually in the periphery of the exposed field, in the region considered least likely to be the site of tumor. The sensitive volume of the counter is introduced into the brain and counts recorded for a statistically significant time interval, usually 0.4 minute, at various depths beneath the surface. We now ordinarily count first at 1 cm. and then at successive increments of 1 cm. to a depth of 4 to 6 cm., as required. The counter is then employed in suspected regions in a similar manner until a sharp increase in counting rate indicates that neoplasm has been struck. After the tumor has been located in this manner, the counter is cleansed with hydrogen peroxide in order to prevent possible spread of malignant cells, and successive approaches are made from normal brain toward tumor in an attempt to demarcate its boundaries. In those instances where radical removal by lobectomy or bloc dissection can be carried out without sacrifice of the

motor cortex or sensory speech area, resection is accomplished, taking a margin of 1 to 2 cm or more from sites where abnormal counts have been obtained

Tables I and II show counting rates obtained with the probe counter in 28 cerebral tumors of various types as contrasted with normal brain in the

TABLE II—*Localization of 14 Other Cerebral Tumors by Means of the Probe Counter, with Attempt at Demarcation for Total Extirpation in Six Cases*

Case	Time in Hours After Injection	Corrected Counts per Minute		Ratio of Counts	Histologic Type	Useful for Demarcation of Tumor
	of P ³²	Tumor	Brain			
W F	18 7	812	114	7 1	Astrocytoma	+
D W	26 2	4182	514	8 1	Astrocytoma	+
H H	65 8	2056	270	7 6	Astrocytoma	+
A T	93 8	777	112	6 9	Astrocytoma	+
W P	15 3	1673	82	20 4	Medulloblastoma	—
A H (2)	61 7	24232	2852	8 5	Astroblastoma	—
B B	16 4	7843	137	57 1	Oligodendroglioma	+
W B (2)	42 2	627	105	6 0	Ependymoma	—
D M	5 7	1650	100	16 5	Unclassified glioma	—
A S	19 7	1337	67	20 0	Unclassified glioma	+
J S	1 8	5226	961	5 4	Unclassified glioma	—
M M	43 5	4523	159	28 4	Angiosarcoma	—
W H	16 5	2136	64	33 3	Metastatic carcinoma	—
G J	19 5	755	26	29 0	Metastatic carcinoma	—

same patient. In five instances, tumor presented on the surface and location by means of the counter was not necessary. In 12 cases data obtained in counting was employed in an attempt to demarcate the tumor in order to facilitate its radical removal.

Figures 2 and 3 illustrate the technic of left (major) temporal lobectomy in case C B (not in Table I), using the probe counter in order to demarcate

TABLE III—*Case C B Demarcation of Glioblastoma with Left Temporal Lobectomy, 241 Hrs after Injection of P³²*

Depth	Counts per Minute	
	3 cm	4.7 cm
B	77	117
A	431	564
C	520	932
E	109	512
D	105	124

the tumor. Point B is in the "control area." Abnormal counts were obtained at depths of both 3 cm and 4.7 cm at points A and C (Table III), while a deep tongue of tumor tissue was demonstrated only at 4.7 cm at point E. Counts were again normal at point D. Resection was carried out through what appeared to be normal tissue, the plane of the incision passing just below



FIG 2—Case C B See Table III Demarcation of glioblastoma prior to left temporal lobectomy



FIG 3—Case C B Appearance of the brain following left temporal lobectomy

the Sylvian vessels and through point D posteriorly. Speech was only temporarily impaired following the procedure, although his subsequent course nine months after operation would suggest that the tumor, a glioblastoma multiforme, was not completely extirpated.

Table IV shows four cases in which a tumor was not localized by means of the counter. We may expect, as in case R H, where virtually the entire cerebral hemisphere was infiltrated by gliomatous cells, to find this method of no value, since no normal area is available for comparison. An occasional small, deep tumor may also be missed, as in cases I C and C E, since the method is effective only when the counter approaches within approximately 5 mm of the tumor. Case G T, in whom no tumor was found, is being followed, but it now appears likely that this patient does not have a cerebral tumor.

TABLE IV—Four Cases in Which No Tumor Was Identified by Means of the Probe Counter

Case	Subsequent Findings	Classification
R H	Diffuse gliomatosis. No normal area was available for control.	Clinical limitation of method.
I C	Counter was introduced to 5.0 cm. Tumor in uncus and peduncle began at 6.5 cm. in P. M. specimen. P. M. ratio 5.8:1.	Error in application of method.
C E	Deep metastatic nodule 1.2 cm. in diameter. Counter missed tumor by 0.5 cm.	Error in application of method.
G T	Patient made complete clinical recovery and has remained well for 9 months.	No tumor. Method presumably correct.

SUMMARY

Radioactive phosphorus, administered intravenously, has been used clinically in order to localize and demarcate brain tumors. Its high concentration in cerebral tumors as compared with normal brain was suspected on theoretical grounds, and now appears to be adequately confirmed. A Geiger-Mueller counter of diameter comparable to that of a ventricular needle has been employed at operation in 33 cases in an attempt to localize intracranial tumors. Data adequate for localization was obtained in 29 cases, in 23 of which the tumor did not present on the surface. In one case, diffuse gliomatosis, the method was intrinsically of no value, and in two cases the method was not adequately employed. In one instance no tumor was located and the clinical course would suggest that none is present.

In 13 cases an attempt has been made to demarcate the tumor for block resection or lobectomy through normal tissue. A later communication will report results and limitations of this method when applied to the radical surgery of the gliomas.

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DISCUSSION—DR FRANCIS C GRANT, Philadelphia, Pa We have attempted to identify intracranial tumors specifically with dye, using Nile blue instead of the fluorescein salt We have not as yet had sufficient experience to speak with any certainty, but in four cases, the tumor was stained definitely and specifically blue, in contradistinction to the surrounding brain Something of this kind, it seems to me, will be of extreme importance in the neurosurgery of the future, because certainly the limitations of these tumors, particularly the infiltrating gliomas, are difficult to determine by the naked eye alone, and unless complete extirpation is possible, a recurrence will, of course, take place

At the present time I am not certain of the importance of these drugs prior to the opening of the skull Even if radioactive material can be attached to the dye which impregnates the tumor specifically and then the area of increased radiated material picked up with a Geiger counter, the value of this method of localization may not be much of an improvement over the use of air However, when once the skull has been opened and the brain exposed, to be able to outline the size of the tumor accurately by contrast staining methods, so that the surgeon can be certain that complete extirpation has been accomplished, is a matter of great importance The only way that a brain tumor can be cured is by total and complete extirpation

There is another possibility inherent in the use of these dyes It was stated that the amount of material taken up by the tumor depended upon the cellularity of the growth If, by the use of these dyes, it would be possible to make a differential diagnosis preoperatively between the very cellular and the relatively acellular types of glioma, this would be important Anything that will lead us to believe that we are dealing with a glioblastoma multiforme prior to operative procedure would save the patient and the neurosurgeon an unnecessary operative procedure If it is possible to make this differential diagnosis with certainty by this method, it will be a long step in advance

CLINICAL USE OF RADIOACTIVE PHOSPHORUS

DR WILDER PENFIELD (Montreal, Canada) The fluorescein method and the use of radioactive phosphorus are studies of great importance. They should be pushed. Neither method has come to a point where it can be generally adopted. The same can be said for the use of the electrocorticogram with the electrodes placed on the cortex. This latter method might locate a neoplasm but biopsy is still needed.

Actually, the application of the two methods described today is only to the infiltrating tumors, not to the benign ones which we can get out and which we can localize by other means, ventriculography particularly. It is still necessary to fall back upon exposure and inspection of the brain.

I have always been very much interested in pathological study, and we always do biopsies of infiltrating brain tumors before removal. Gross inspection is usually sufficient to indicate the situation of neoplasm but biopsy must be relied upon for prognosis.

DR GEORGE E. MOORE (Minneapolis, Minn.) I do think that sodium fluorescein can be used to good advantage clinically. Dr. W. T. Peyton and Dr. Lyle French of our clinic have found it helpful especially in the localization of tumors whose position has not been completely elucidated by ventriculography.

As to radioactive diiodofluorescein, I think it is more important as a research tool than as a diagnostic measure at the present time. This technic should be quite valuable in the future for the study of other diseases of the central nervous system as those studied by Dr. Robert B. Airs (*ie* amyotrophic lateral sclerosis) and others which are intimately associated with damage to the so-called blood-brain-barrier. Among these diseases might be certain forms of epilepsy. In the latter instance, sodium fluorescein may be of some value for the localization of epileptogenic loci that cannot be determined readily by ordinary visual means.

DR B. SELVERSTONE (Boston, Mass.) I should like to thank Dr. Grant and Dr. Penfield for their discussion. May I say, however, that in our hands, since we have had a lot of experience with the technic, we have found this to be a practical clinical tool of great value. I should like to tell of one case which may point this out.

One month ago a patient was admitted to the private service with signs and symptoms of a cerebellar tumor apparently in the right hemisphere. After ventriculography and other studies, which confirmed the presence of a cerebellar tumor, operation was carried out. The cerebellum was explored and was found to be entirely normal in appearance. The aqueduct was patent. The wound was closed.

The patient proceeded to do very poorly. He developed papilledema which had not previously been present, and his flap bulged considerably. One week ago he was given two millicuries of radioactive phosphorus. On the following day he was taken to the operating room, his flap was reopened, the cerebellum exposed, and again it appeared to be entirely normal.

(Slide) This slide shows the findings with the Geiger counter. It was introduced first into the left lobe of the cerebellum, and you can see the counts at 1, 2, 3, 4 and 5 cms. It was then introduced into three places in the right cerebellum hemisphere, and again you can see the counts. Notice that these counts are all rather low—from 14 to 176 counts per minute. No tumor was found.

The counter was next introduced into the vermis. At 1 cm there were 304 counts per minute. At 2 cms there were 1080 counts, and so on up to 4 cms, where 1560 and 2136 counts were obtained in two loci. In the vermis at a depth of a little over 1 cm a large glioma was encountered, and a subtotal removal was undertaken. Since that time the patient has done reasonably well.

EVALUATION OF TOTAL SYMPATHECTOMY*

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IN THE EVOLUTION OF OPERATIONS on the sympathetic nervous system for the treatment of hypertensive vascular disease a dictum frequently proposed has been that the degree of success is proportional to the extent of the sympathectomy. This assertion has some times been tempered by adding that the purpose of the operation should be the denervation of as large an area of the body as is necessary yet reasonably safe. The earlier types of limited operation came to be largely supplanted by the thoracolumbar resection from the eighth or ninth thoracic to the upper lumbar levels proposed by Smithwick¹ ten years ago. Peet² changed to a higher resection of the thoracic sympathetic in his supradiaphragmatic operation. More recently others (Poppen,³ and Hinton and Lord⁴) have extended the resection of the thoracic chain up to the third or fourth thoracic ganglia and have implied that blood pressure lowering effects were better. A logical conclusion would seem to be that consistently good results might be expected if total sympathectomy were performed, providing, of course, the patient could tolerate the operation and not be left a "homeostatic cripple." Grimson⁵ reported before this Society eight years ago his performance of total paravertebral sympathectomy in three patients and he has presumably added to this number since.

Since neither the etiology of hypertension nor the mechanism by which sympathectomy exerts its beneficial effects are known, proof for the superiority of one type of operation over another should rest on the comparison of results. However, the unpredictable nature of hypertension makes the evaluation of any form of treatment difficult and it is even more troublesome to try to measure the relative merits of different types of operation. In this report, which deals with the results of total paravertebral sympathectomy in 30 hypertensive patients, some comparative statistics have been included for whatever value they may have. Also, an attempt has been made to estimate the effects of successively more extensive sympathectomy in the same patient. Some of the mechanisms responsible for the beneficial effects of total paravertebral sympathectomy, and some of the reasons for its failure to accomplish all that might have been expected, are reviewed in the light of these data.

Material—The patients in this series of 30 were each selected for total paravertebral sympathectomy because it was felt that some complicating factor or factors in their hypertensive disease would be more likely to respond to a wider sympathectomy than has usually been employed in this clinic (Ray⁶). It should be evident that the majority were poorer operative risks.

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Study supported by a grant from the John & Mary R. Markle Foundation.

than obtains in the general average of hypertensive patients subjected to sympathectomy. Patients with angina pectoris (17) and patients with retinal hemorrhages or papilledema (Groups III and IV retinopathy, according to the classification of Keith, Wagener & Barker⁷) constitute the bulk of the series, some of these also had vasospastic states of the extremities or palpitation and tachycardia. The remainder had only vasospastic disorders, tachycardia and palpitation as initial symptoms in their disease, or following the thoracolumbar type of operation.

Of the six patients who had thoracolumbar (T8-L3) sympathectomies previously, one had little improvement in blood pressure and angina and later developed retinal hemorrhages. Two had a persistence of their severe angina pectoris and a return of blood pressure to preoperative levels. One had a persistence of mild angina, and developed tachycardia, palpitation and Raynaud's phenomenon of the upper extremities. One had Raynaud's phenomenon in the hands, tachycardia and palpitation, but a good lowering of blood pressure in response to thoracolumbar sympathectomy.

Of the 24 patients in whom total sympathectomy was done as a primary procedure, nine had Group III retinopathy and 11 had Group IV, ten of these patients also had angina pectoris. The remaining six patients had Group II retinopathy, of which three had angina pectoris, one had scleroderma and one, a 53-year-old man, had a fixed diastolic pressure of 150 mm of mercury.

The pertinent data regarding these patients are tabulated in Table I and summarized in Table II.

Method of Operation—The operation of total bilateral paravertebral sympathectomy from stellate to the third lumbar ganglia was carried out in two, three and four stages in this series. For the 24 patients in whom the total operation was planned initially, a two-stage operation (one side at a time with an interval between varying from two to four weeks) was performed in eight patients. In 16 the operation was carried out in three stages, employing a total sympathectomy on one side first, next a thoracolumbar (T7 or 8 to L3) on the other side in about two weeks, and finally a completion of the thoracic sympathectomy on the second side, usually in two weeks. But in six patients it was found desirable to delay the final stage for three to 16 months.

For six patients who had previously had thoracolumbar (T7 or 8 to L3 and splanchnic nerve) sympathectomy the remainder of the thoracic sympathetics, including the stellate ganglia, were removed in one bilateral operation in three patients and in two operations in the other three. The time interval between the thoracolumbar operation and completion of the total sympathectomy was 12 to 30 months. Together with their original operations these patients had a total of two, three or four separate operations.

The anesthesia employed in all operations was endotracheal ether and oxygen preceded by intravenous pentothal induction. The operative approach to the sympathetics was retroperitoneal and retropleural. The thoracolumbar

part of the operation employed resection of the proximal ends of the eleventh and twelfth ribs, detachment of the diaphragm, and incision in the lumbar fascia. Through this exposure the lumbar chain was resected to a point below the contribution of the third lumbar rami, and the thoracic chain together with the great splanchnic nerve was freed to a point above the contribution of the seventh or eighth thoracic rami. The thoracic sympathetics were divided here unless the operation was to be completed at once, in which case they were tucked into the upper part of the exposed paravertebral gutter and the

TABLE I—*Preoperative Data, Type of Operation, Postoperative Data and Period of Observation After Total Sympathectomy in 30 Patients. Changes are Graded Slight (sl), Moderate (mod), and Marked (mk). T-L-Thoracolumbar Sympathectomy*

PREOPERATIVE DATA											
Patient No	Sex	Age	Diastolic Blood Pressure	Eye Ground Group	Angina Pectoris	Enlarge ment of Heart	E K G Changes	Cardiac Failure	Renal Impair ment	Cerebral Involvement	Degree of Disability
1	M	32	170	IV	0	0	Mod	0	Mod	0	Mk
2	M	34	160	IV	+	Sl	Mod	Mod	Sl	0	Mk
3	F	29	170	IV	+	Sl	Sl	Sl	0	Sl	Mk
4	F	31	160	IV	+	Sl	Mod	Mod	Mod	0	Mk
5	M	48	170	IV	0	Sl	Sl	0	0	0	Mk
6	M	40	140	IV	0	Sl	Sl	0	0	0	Mk
7	M	43	160	IV	0	Sl	Sl	0	Sl	0	Mod
8	F	31	120	IV	0	0	0	0	Mod	Mod	Mk
9	M	43	170	IV	0	Sl	Sl	0	Sl	0	Mk
10	F	38	124	IV	0	Mod	Sl	Mod	0	0	Mk
11	F	49	140	III	0	Sl	Sl	0	0	Mod	Mod
12	F	47	130	III	+	Sl	Sl	0	0	0	Mod
13	F	40	120	III	+	Sl	Sl	Sl	0	0	Sl
14	F	40	130	III	+	Mod	Mod	Sl	0	0	Sl
15	M	48	150	III	0	0	Sl	Sl	0	0	Mod
16	M	48	140	III	0	Mod	Sl	0	0	0	Sl
17	F	45	140	III	+	Sl	Sl	0	0	0	Mod
18	F	50	170	III	+	Mk	Mk	Mod	Sl	0	Mk
19	M	53	150	II	0	Mod	Mod	Sl	Sl	0	Mod
20	M	45	120	II	+	0	Sl	0	0	0	Mod
21	M	43	110	II	+	Sl	Sl	0	0	0	Sl
22	F	37	160	III	+	Sl	Sl	0	0	0	Mod
23	F	32	150	II	+	Mod	Mod	0	0	0	Mod
24	F	45	120	II	+	Mod	Mod	Sl	0	0	Mod
25	M	42	110	II	+	Sl	Mod	0	0	0	Mod
26	F	28	90	II	0	0	Sl	0	0	0	Sl
27	F	44	120	II	0	Sl	Sl	0	0	0	Sl
28	F	51	160	IV	+	Mod	Mod	Sl	0	Mod	Mk
29	M	52	150	III	+	Sl	Sl	Sl	0	0	Sl
30	F	49	160	II	+	Mod	Mod	Sl	0	0	Sl

wound closed. A second incision for removal of the remainder of the thoracic sympathetics was made parallel to the spine to permit resection of the proximal several centimeters of the third, fifth and sixth ribs. After reflection of the pleura through this exposure the ganglionated chain was freed from the stellate to the sixth or seventh thoracic ganglia, as the case required. In the one-stage operation the entire ganglionated chain from stellate to L₃ ganglia, with the attached splanchnics (and sometimes the celiac ganglion), could be lifted out intact. The celiac ganglia were removed on both sides in eight patients and on one side in two.

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Patients were placed on the operating table in the lateral position, slightly tilted forward for both the upper and lower incisions, except for two patients placed in prone position on the "cerebellar" table for the performance of bilateral upper thoracic sympathectomy. The average time required for the performance of a one-stage total sympathectomy on one side was two hours. During the operation patients received intravenous 5 per cent glucose in water, sometimes supplemented by blood transfusion and neosyneprine, one or both

TABLE I—(Continued)

POSTOPERATIVE DATA						
Patient No	Operations	Diastolic Blood Pressure	Fall in Diastolic Blood Pressure	Eye Ground Groups	Degree of Rehabilitation	Follow-up Period
1	2 stage total with celiac gangl	120	50	II	Mk	2 years
2	3 stage total	140	20	II	Mk	2 years
3	2 stage total	120	50	II	Mk	2 years
4	2 stage total with celiac gangl	150	10	II	Mk	2 years
5	2 stage total	114	56	II	Mk	2 years
6	3 stage total	100	40	II	Mk	2 years
7	3 stage total with celiac gangl	90	70	II	Sl	2 years
8	3 stage total	120	0	II	Mk	2 years
9	2 stage total with celiac gangl	130	40	II	Mk	1½ years
10	3 stage total	100	24	II	Mod	1½ years
11	3 stage total with celiac gangl	120	20	II	Mod	2 years
12	3 stage total	110	20	II	Mk	2 years
13	2 stage total	90	30	II	Mk	2 years
14	3 stage total	110	20	II	Mk	2 years
15	3 stage total	120	30	II	Mod	1½ years
16	3 stage total with celiac gangl	100	40	II	Mk	1½ years
17	3 stage total	88	52	II	Mod	1½ years
18	3 stage total	110	60	II	Mod	1 year
19	3 stage total	100	50	II	Mk	2½ years
20	3 stage total	90	30	II	Mod	1 year
21	2 stage total	90	20	II	Sl	1 year
Prev T-L						
22	27 mos —1 stage upper thoracic	160	0	II	Mk	2½ years
23	12 mos —1 stage upper thoracic	130	20	II	Mk	2½ years
24	26 mos —2 stage upper thoracic	100	20	II	Mod	2 years
25	12 mos —2 stage upper thoracic	120	0	II	Mk	2 years
26	20 mos —1 stage upper thoracic	70	20	II	Mod	2 years
27	30 mos —2 stage upper thoracic	80	40	II	Mod	2 years
28	3 stage total	Died after 11 months				
29	2 stage total	Operative death				
30	3 stage total	Operative death				

Mortality—Among the 30 patients, two deaths occurred as a result of operation (6.3 per cent). One of the patients (No. 30) had a high grade of hypertension and angina pectoris, and died on the operating table at the end of a third-stage operation, presumably of heart failure. The other patient (No. 29) had angina pectoris and advanced retinopathy, he died of a painless coronary infarction 24 hours after completion of the second stage of a two-stage operation.

One other patient (No 28) died suddenly at home 11 months after operation, presumably of cardiac failure due to coronary disease. She had been relieved of angina pectoris and otherwise improved after operation.

Postoperative Complications—Pleural effusion was the most frequent complication after operation, due, it is believed, to the extensive manipulation of the pleura and to the high incidence in this series of borderline cardiac decompensation. It occurred in nine patients, and in four, one or more aspirations of the effusion were required. In most of the patients digitalization and the administration of mercurial diuretics were of value.

Cardiac failure occurred after unilateral total sympathectomy in three patients with borderline cardiac compensation but there was quick improvement following the use of digitalis, oxygen therapy and mercurial diuretics.

TABLE II—*Grouping of 30 Cases of Total Sympathectomy According to Grade of Hypertension and Accompanying Symptoms*

	No. of Cases
Advanced grade of hypertension	21
With Group III retinopathy	10 cases
With Group IV retinopathy	11 cases
Of these 11 had angina pectoris	
Angina pectoris and less advanced hypertension (Group II retinopathy)	6
Less advanced hypertension	3
With Raynaud's phenomenon and tachycardia	2 cases
With scleroderma	1 case
Total	30
In six of the 30 cases there were intervals of one to two and one half years between thoracolumbar and total sympathectomy. Conditions leading to additional operation were:	
Angina pectoris	3 cases
Angina pectoris and retinal hemorrhages	1 case
Raynaud's phenomenon	2 cases

As a result of this experience early in the series, digitalis was used preoperatively more commonly thereafter when there was any question of the state of the cardiac reserve.

One patient (No 3), a 29-year-old woman with advanced hypertension, became comatose shortly after reacting from anesthesia following the second stage of a two-stage sympathectomy. The temperature rose to 41°, there were shifting neurologic signs, and consciousness was not regained for eight days, the spinal fluid during this period was normal. She eventually made a good recovery. The complication is thought to have resulted from anoxia to the brain during the operation and thereafter, during a period of low blood pressure.

The course of convalescence and degree of rehabilitation after operation varied widely but on the whole the variations were not significantly different after the lesser operation of thoracolumbar sympathectomy. The measure of rehabilitation is indicated in Table I.

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THE EFFECTS OF THE OPERATIONS ON THE HYPERTENSIVE STATE

Excluding two patients who died in the hospital and one who died before the end of a year, 27 were repeatedly examined from one to two years after operation, and the latest postoperative observations are the ones recorded in the comparative pre- and postoperative evaluation. Table I provides much of the data in tabular form.

Effects on Blood Pressure—The effect of the operation on blood pressure is interpreted by comparing the average preoperative reclining diastolic pressure with the highest postoperative diastolic pressure. In the surviving 21 patients who had initial total sympathectomy there are nine (43 per cent) who now have diastolic pressures consistently of 100 or less mm of mercury, the remaining 12 all had some lowering of their diastolic pressure, and at least six may be said to have had a significant lowering to a much safer level.

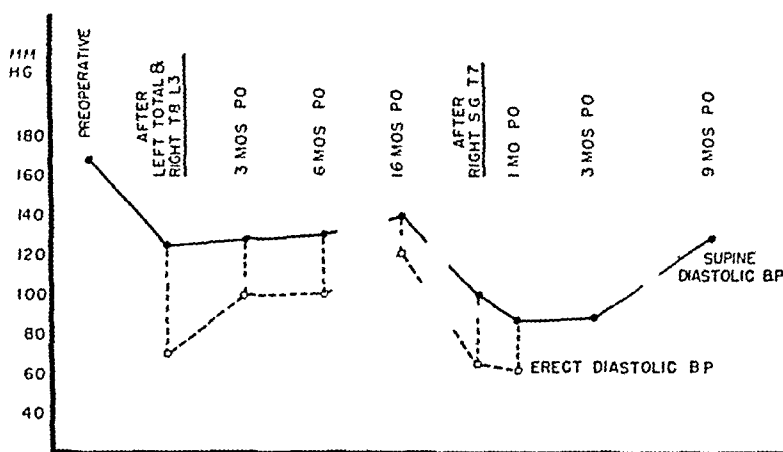


FIG 1—Patient No. 18. Effect on diastolic blood pressure of total sympathectomy after the first two stages (lt stellate to L3 and rt T8 to L3) and after delayed third stage (rt stellate, S G, to T7).

than originally existed. This record is perhaps better than might be expected from the thoracolumbar operation, but the number of this series is small and the types of cases make comparison unreliable.

In six of the 21 patients who had "initial" total sympathectomy there was a lapse of from three to 16 months between the second and third stages of the operation, that is, before the final resection of the remaining portion of the upper thoracic chain on one side. Figure 1 shows the effect on diastolic blood pressure and postural hypotension after a delayed third stage of a total sympathectomy in patient No. 18. In all of these patients there was an additional fall in diastolic pressure of 20 mm of mercury, or more, and an increase in postural hypotension. In three the effect was transient but in the other three some lowering has persisted for a year or more. There was no apparent difference in the effects of resecting the right or left thoracic chain. Thus the results in these several patients indicate that there may in some be a greater lowering of blood pressure with more extensive sympathectomy.

The graded sympathectomy in the six patients who had a bilateral thoracolumbar (T7 or 8 to L3) operation one to two years before completion of a total sympathectomy is of added interest. In three of these patients there was no significant decrease in the blood pressure after the thoracolumbar operation, following completion of the total sympathectomy the diastolic pressure was not affected in one, it was lowered twenty mm but still high in one, while in the third it was lowered 20 mm, so that the highest diastolic pressure was 100 mm of mercury. In two of the six patients the thoracolumbar operation resulted in moderate lowering of the pressure, and following completion of the total sympathectomy the diastolic pressure was unchanged in one and lowered to normal (120/80) in the other. In one of the six patients the thoracolumbar operation resulted in a normal blood pressure (220/120 reduced to 140/90) and after completion of the total sympathectomy, performed for relief of disagreeable vasospasm in the upper extremities and tachycardia, the pressure was lowered still further (to 110/70).

Therefore, the evidence indicates that total sympathectomy has a greater effect in lowering blood pressure than a lesser resection of the sympathetics in some patients. In this series a poor or mediocre result after thoracolumbar operation was improved in 50 per cent of the patients by adding the excision of the remaining sympathetics. But the fact remains that a total sympathectomy, even when initially performed, does not always lower the resting blood pressure significantly, and indeed may not lower it at all. Additional interesting facts come to light in regard to the effects of graded sympathectomy in the studies with tetraethylammonium chloride, and in a study after bilateral anterior rhizotomy (T12, L1 and 2) was performed in one patient with a total sympathectomy (see following).

Effects on the Heart—Two important effects on the heart result from the addition of the upper thoracic sympathectomy to the thoracolumbar operation, providing the excision is carried high enough to include the first thoracic (or the stellate) ganglia bilaterally. These effects are abolition or improvement in cardiac pain by interruption of the afferent nerves that traverse the sympathetics, and slowing of the cardiac rate by interruption of the accelerator nerves. It is believed that the nerve fibers for each of these functions traverse the stellate to the fourth or fifth thoracic ganglia bilaterally.

Angina pectoris unquestionably existed in 17 patients of the series. Four of the six patients who came to total sympathectomy a year or more after thoracolumbar operation had angina pectoris. One patient developed his pain after the first operation, but the other three originally had angina and were unrelieved by the operation. This has been a common experience in patients with angina pectoris having thoracolumbar sympathectomy, even in those with lowered blood pressure. In most of the 17 patients the pain occurred chiefly with effort, but in five the pain imposed definite limitations on their activity. The three patients who died all had angina pectoris. All of the 14 who survived were relieved of pain in the chest and arms, and their capacity

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for exercise was increased, but three had occasional and moderate pain in the neck and jaws on exertion. One of these had pain in the neck, in addition to pectoral pain, before operation while the other two developed their cervical pain some time after operation. In case the preoperative pain was unilateral the first stage of the operations was usually planned to sympathectomize that side. In support of past experience that unilateral sympathectomy may be inadequate for relief of unilateral angina pectoris, two of these patients developed a similar pattern of pain on the opposite side during the period of delay before the final operation was performed.

Tachycardia and the palpitation that accompanies it have, in those patients who possessed it, been uniformly relieved by total sympathectomy. Several patients had a relative tachycardia before operation, but two of the patients who had previously had a thoracolumbar operation were greatly distressed by these symptoms, particularly on changing from a horizontal to an erect

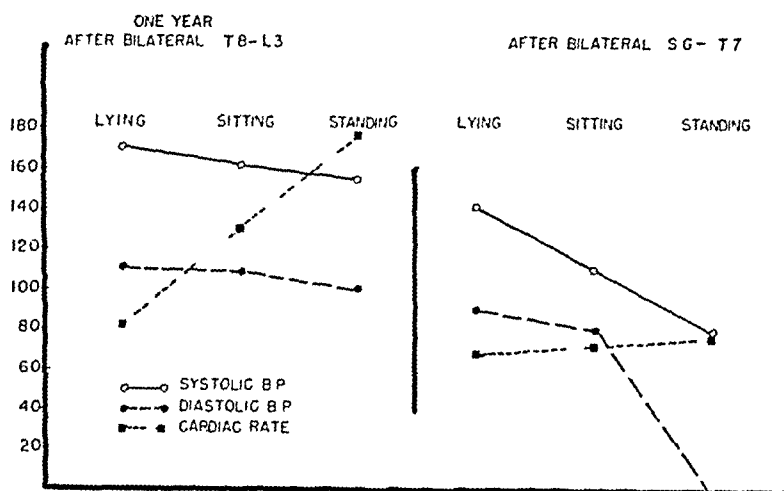


Fig 2—Patient No 25 Effect on tachycardia and blood pressure of adding bilateral upper thoracic sympathectomy (stellate ganglion, SG, to T7) one year after bilateral thoracolumbar sympathectomy (T8 to L3)

posture, or on exercising. This is a common finding in the early postoperative period after the thoracolumbar operation, when postural hypotension is marked. In a few patients it persists in some degree with change in position, or with exercise, even when postural hypotension has largely or wholly subsided. For example, (Fig 2) one patient (No 25) a year after thoracolumbar sympathectomy consistently had a change in blood pressure from 170/110 to 155/100 on rising from a horizontal position, and simultaneously an increase in cardiac rate from 82 to 176 per minute. Paradoxically, during the early period following completion of the total sympathectomy (by bilateral upper thoracic sympathectomy) the blood pressure fell from 140/90 to 80/70 on changing posture, and simultaneously the cardiac rate changed from 68 to 76 per minute.

All patients showed bradycardia after completion of total sympathectomy. The rate fell to a level between 40 and 60 per minute, the maximal slowing usually occurring on the second to fourth day after operation. Consistent slowing of the rate was not observed after a unilateral thoracic sympathectomy of either side. While there was some recovery from the maximum bradycardia with the passage of time in most patients, relatively slow resting cardiac rates and failure of tachycardia to develop with postural hypotension or exercise persisted in all patients.

The question of whether cardiac efficiency may be embarrassed when postural hypotension occurs without compensatory increase in cardiac rate may aptly be raised. The studies necessary to settle the question are not completed, but certainly it may be said that after a suitable period of post-operative adjustment passed patients did not show impressive outward evidence of cardiac deficiency under these circumstances.

Other Effects on the Hypertensive State—The 21 patients with advanced retinopathy, namely, retinal hemorrhages, exudates and papilledema, all showed a subsidence of these changes within one to three months after the completion of any combination of bilateral operation, even though a third stage was sometimes delayed for a longer period. This alteration in eyeground changes is not peculiar to total sympathectomy but occurs also in the less extensive thoracolumbar operation. However, one case in the series (No. 22) developed retinal hemorrhages two years after a thoracolumbar operation, and following the additional operation converting the partial to a total sympathectomy, the hemorrhages subsided.

The improvement in symptoms, particularly headache, seemed to be of the same degree as that reported for less extensive sympathectomies, although it must be said that the average period of convalescence and recovery from operative symptoms took on the average several weeks longer after total sympathectomy than is required after lesser operations. With regard to headache, a suggestion was made, in a report of results after thoracolumbar sympathectomy (Ray⁶), that part of the reason for improvement might be due to a compensatory vasoconstriction of the extracranial branches of the carotids which counteracted the dilatation and lability thought to give rise to headache. After total sympathectomy these vessels should not be in a state of increased tone, but at least should have been deprived of lability in tone which might be expected to be just as effective.

All but two of the patients who survived operation were rehabilitated to the degree that they either resumed wholly or in large part their former occupations and activities, or else led a fairly active existence within moderate restrictions. In Table I, rehabilitation has been indicated as "marked" or "moderate," respectively. By comparison with the evaluation of the degree of their disability prior to operation in the same table, the results are impressive. The two exceptions were both patients who were virtually invalids prior to operation, but neither was made any more so by the operation.

Comparative statistics of survival in a series as small as this and followed for such a short period of time are not truly helpful. Published results^{2, 6} of partial sympathectomy show impressive benefit in the matter of survival of patients with advanced hypertension, Groups III and IV retinopathy of the Keith, Wagener & Barker classification, when compared with the latter's published results⁷ of survival in similar patients not treated by operation. It will be more important eventually to determine whether more extensive sympathectomy can improve on the results of the thoracolumbar operation. Table III shows certain survival statistics for advanced grades of hypertension the first year after medical treatment,⁷ after the Peet operation of bilateral lower thoracic sympathectomy,² after bilateral thoracolumbar (T8-L3) sympathectomy⁶ and after total sympathectomy. The statistics for the last two types of sympathectomy are from this clinic, and are not significantly different, particularly if the higher operative mortality attending the total

TABLE III—*Comparison of Percentages of Deaths at the End of One Year in Advanced Hypertension (Groups III and IV Retinopathy) Treated by Different Methods*

	No. of Cases	Percentage Mortality at End of 1 Year Retinopathy Groups		
		Group III	Group IV	Combined Groups III and IV
Keith, Wagener and Barker Medically treated	13	35%	79%	69%
Peet Lower thoracic sympathectomy	143		46%	
Ray Thoracolumbar sympathectomy	88	10%	18%	14%
Present series Total sympathectomy	21	10%	79%	95%

sympathectomy were to be taken into consideration, but the results in both these series appear better than those reported following the less extensive Peet operation.

EFFECTS OF THE OPERATION ON HOMEOSTASIS

The coordination of the body as a whole to meet changing conditions in internal and external environment by autonomic adjustment has been called homeostasis by Cannon⁸ (1929). Cannon,⁸ and McDonough⁹ (1939) demonstrated that totally sympathectomized cats and dogs survived under the conditions of the controlled environment of the laboratory, but were unable to make the rapid adjustments which occur in normal animals under conditions of stress, such as extremes in environmental temperature and emotional excitement.

After total sympathectomy in man, the most noticeable effects result from the alteration in vasomotor and sudomotor activity. In the early period after completion of the operation, extremes of temperature are not well tolerated,

and hot weather particularly may be enervating, but by adjustment of clothing and regulation of activity the moderate extremes of temperature occurring in a temperate climatic zone do not afford any great problem in adjustment. The hypotension and its symptoms of giddiness and weakness that accompany change in posture and exercise may be profound soon after operation, and are often of greater degree than that seen following thoracolumbar sympathectomy. There is a sense of obstruction in the nasal passages due to engorgement of the nasal mucosa. The Horner's syndrome may be such that the patient is distressed by his inability to open his eyelids more widely and by the uncomfortable sensation that results from suffusion of the conjunctival blood vessels. Yet within a relatively short time the degree of these symptoms and signs begins to subside and somehow the body makes a progressive adjustment.

The possible means of adjustment are several, and have been commonly thought to be due to sensitization, increase or augmentation in the tone of smooth muscle, and to ready regeneration of sympathetic nerves. Sensitization has been said to occur more readily following postganglionic denervation. In this series there were no discernible differences in the results in the ten patients in whom celiac ganglionectomy was added to the total excision of the ganglionated chains. The possibility that the development of automatic tone in smooth muscle may play some role cannot readily be dismissed, but the bugaboo of regenerating sympathetic nerves needs to be dispelled. The evidence collected from the study of the cases in this series and others gives strong support to the likelihood that the partial return of homeostasis after total paravertebral sympathectomy is due to the presence and augmented activity of residual sympathetic nerves, already present, which do not traverse the paravertebral ganglionated chains, splanchnic nerves or celiac ganglia.

RESIDUAL SYMPATHETIC PATHWAYS

All patients, following paravertebral sympathectomy, whether it is partial or complete, show a predictable loss of sympathetic activity in such measurable functions as skin temperature, sweating, vasodilatation and electrical skin resistance. At first the loss of these functions is complete, but within a matter of days or weeks, long before regeneration of sympathetic nerves could occur, every patient begins to develop recognizable signs of sympathetic activity, which increase with the passage of time and the inherent necessity for the body to utilize whatever compensatory mechanisms remain.

In a previous report¹⁰ residual sympathetic pathways were described innervating the T12 to L3 dermatomes after thoracolumbar (T8-L3) sympathectomy and also in a few cases after total paravertebral sympathectomy. The matter was explored in considerable detail, and it was shown conclusively that the return of sympathetic activity in these dermatomes, namely in the groins and anterior half of the thighs, could be initially prevented or subsequently corrected if anterior rhizotomy from T12 to L2 inclusive was performed in conjunction with the paravertebral lumbar sympathectomy. This

earlier work raised the possibility that similar pathways were responsible for return of activity in the face, upper extremities, trunk and the lowermost sacral dermatomes. It was postulated that the ganglia for the postganglionic fibers in the residual pathway to the T12-L3 dermatomes were either in the spinal nerves or closely associated with them. Later it was of great interest to find that the previous work of Wreite¹¹ and Skoog¹² had already demonstrated microscopic masses of ganglion cells distributed in communicating rami to spinal nerves and often in close proximity to the latter. Even though the function of these ganglia was not established it was believed that they were motor (sympathetic) cells. It was also of interest that the ganglia were found in greatest abundance in the cervical and lumbar regions, although

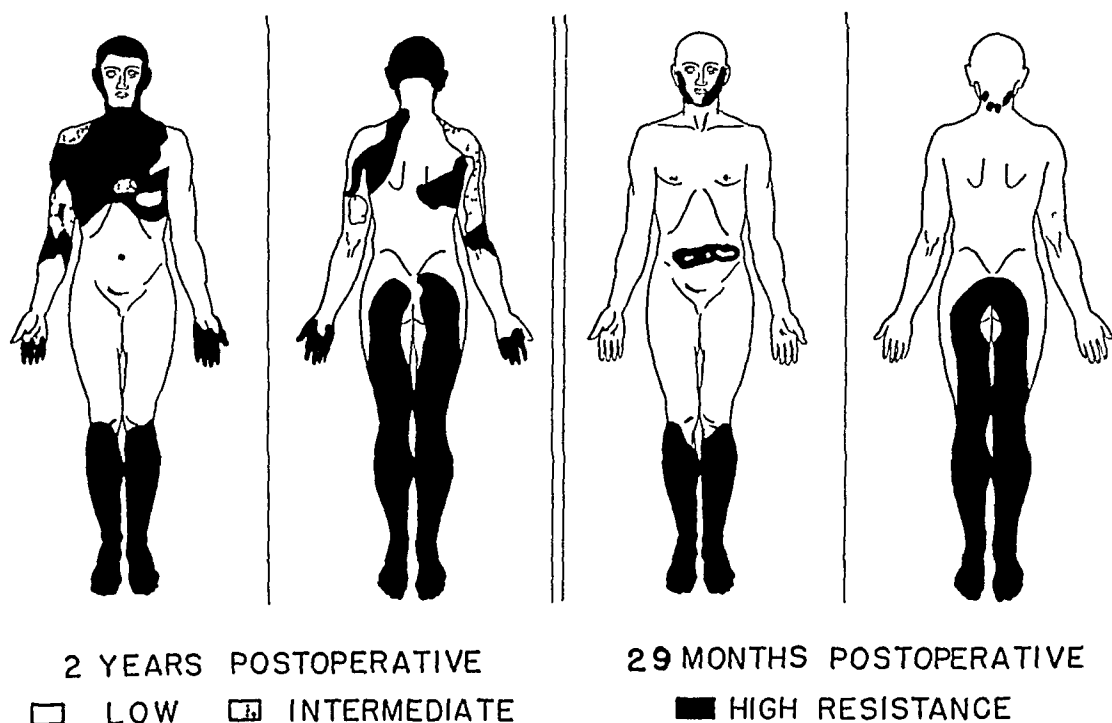


FIG 3—Patient No 8 (Left) Skin resistance pattern 24 months after total sympathectomy Patient No 23 (Right) Skin resistance pattern 29 months after total sympathectomy

similar ganglia were present in all the thoracic spinal nerves. More recently, sympathetic ganglion cells in ventral roots have also been described by Alexander, Kuntz, Henderson and Ehrlich.¹³

Patterns of Skin Resistance—The patterns of skin resistance over the entire body 24 and 29 months after total sympathectomy in two patients is illustrated in Figure 3. The areas of low resistance indicate the presence of centrally controlled sympathetic activity, and all patients of this series showed similar patterns some months after operation. On the whole, the return of function was most rapid and uniform in the T12 to L3 dermatomes and in the central area of the face, where the patterns were symmetrical and nearly super-imposable from patient to patient. Sympathetic activity returned more

slowly in spotty areas over the upper extremities and trunk, where the patterns were less symmetrical and less constant. The final patterns in the upper extremities and trunk did not conform to any segmental arrangement, and varied considerably on the two sides in the same patient. It does not seem reasonable to attribute this non-segmental and asymmetrical return of function, after similar types of sympathectomy have been performed on the two sides, to sensitization, regeneration or any other of several suggested mechanisms except activation of already existing nerve pathways. Skoog's¹² work has shown that there are marked differences in the number and precise location of the accessory ganglion cells in the cervical region in different patients and on the two sides in the same patient.

Complete and permanent sympathectomy in the upper extremity has not yet been accomplished by any of the operations in common practice, nor has a single instance occurred in which the trunk has remained completely denervated after total sympathectomy. The irregular and inconstant late patterns of skin resistance in the upper extremities are in marked contrast to those in the lower extremities, where the pattern is constant and where rarely if ever is there any evidence of resumed function below the knees. This difference in the upper and lower extremities is in full accord with the common clinical experience that sympathectomy employed for the treatment of vasospastic states is uniformly better in the feet than in the hands.

The usefulness of electrical skin resistance determinations as a method of identifying sympathetic activity has been soundly established by Richter's¹⁴ work. But on the surface areas of the body where the residual innervation is great enough, sweating, pallor, or mottling of the skin and diminished temperature are often easily demonstrated. Sweating and mottling of the skin occur in varying degree in such areas, the degree apparently depending on the number of residual ganglion cells supplying the area, and the need for the organism to compensate for impairment of sympathetic activity in other parts of the body. For example, it is common to see cold hands, pallid fingers, mottling of the arms, and increased sweating in the upper part of the body after thoracolumbar (T8-L3) sympathectomy has deprived lower portions of the body of vasomotor and sudomotor functions. When larger areas are deprived of function by total sympathectomy compensatory activity is greatly augmented in any region where residual innervation exists. This is exemplified by the excessive sweating which occurs in the anterior thighs and groins particularly during the early months after total sympathectomy. This region (T12-L3 dermatomes) appears to be the most richly supplied by residual pathways of any in the body. Excessive sweating similarly occurs in a band in the lower thorax, if in performing a total sympathectomy a two-stage operation on one side fails to meet and the sixth or seventh thoracic ganglion is left intact, as has occasionally occurred.

It has often been observed though not easily explained that after sympathectomy the resumption of demonstrable sympathetic activity in predictable

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areas supplied by residual nerves is delayed in its appearance. Even when a single midthoracic paravertebral ganglion is left in place in an otherwise total sympathectomy the thoracic dermatome supplied by the ganglion appears for several days or weeks to be sympathectomized also. Then, sweating begins to appear, and it increases gradually in amount until the skin of that dermatome may be dripping. This phenomenon more than any other meets the objection of those who maintain that if residual pathways do exist, the evidence of their presence should be manifest immediately after operation.

Other Clinical Evidence—In at least three patients of this series cramping pains in the anterior thighs developed on exercising after total sympathectomy, even though intermittent claudication had not existed before

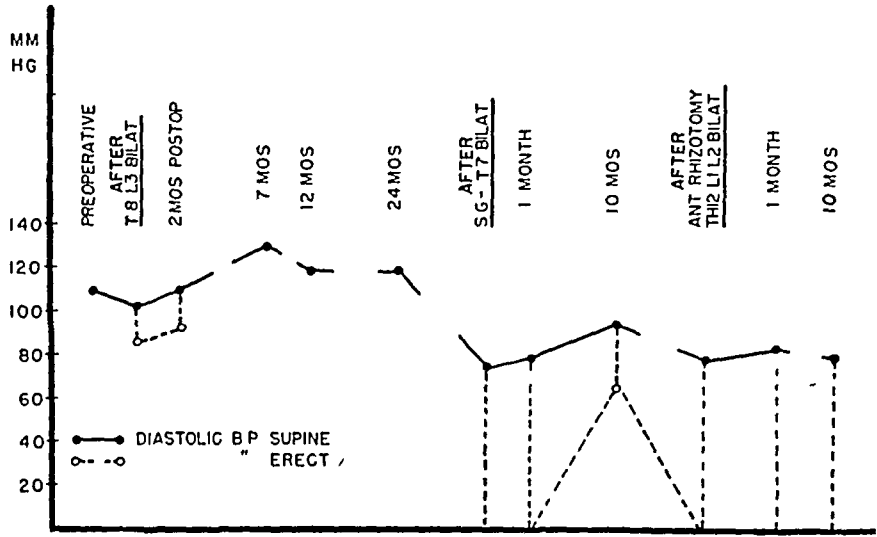


FIG 4—Patient No 24. Effect of graded sympathectomy on blood pressure, particularly emphasizing the additional effect of anterior rhizotomy ten months after total paravertebral sympathectomy

operation. Since the surface areas of the anterior thighs possess a residual sympathetic innervation it was reasoned that the vasculature of the thigh muscles might be spastic in compensation for extensive vasodilatation elsewhere in the body, and this in turn might lead to pain on muscular effort. Accordingly, in one of these patients (No 24) anterior rhizotomy, T12 to L2 bilaterally, was performed. At the time of operation direct faradic stimulation of each of these roots caused a transient alteration of skin resistance in the homolateral anterior thigh. The result of the operation was abolition of the cramps as well as loss of sympathetic activity on the surface of the T12 to L3 dermatomes, and the effect may be assumed to be permanent. In this same patient (Fig 4) the anterior rhizotomy had an additional effect on postural hypotension and to a lesser degree on the blood pressure in the supine position.

The lowest spinal segmental extent of the sympathetic system from this and previous studies has been found to be L3. The highest spinal segmental

extent has not been definitely established, though it has been assumed in the past to be T1 or possibly C8, the ramus from which connect with the stellate ganglion. The consistent appearance of sweating in the face after total sympathectomy, including the stellate ganglion, has raised the question as to the mechanism. The question remains unsettled, but there are other experiences to suggest that sympathetic innervation to the pupil and levator of the upper lid has segmental origins above the eighth cervical. As illustration, 18 months after completion of total sympathectomy, including removal of the stellate ganglia, a patient was found to have greater ptosis and miosis on the left side, some degree of asymmetry being common in such cases. The entire remaining cervical sympathetic chain was then removed on the right side, which resulted in a persistent inequality in ptosis and miosis, but now greater on the right side. Unless it be assumed that regenerating preganglionic fibers from thoracic levels joined the cervical chain, which is believed to be unlikely, it must be reasoned that preganglionic fibers arise from cervical segmental levels.

It can probably be shown that preganglionic cervical fibers to the upper extremities which do not traverse the ganglionated chain also exist. This postulation is given support by the finding that following paravertebral thoracic sympathectomy, including the stellate ganglion, supplemented by intraspinal division of the first three thoracic anterior nerve roots, there is still evidence of residual sympathetic activity in the extremity.

In the face of the evidence of the importance of other sympathetic pathways that remain after any type of sympathectomy, including total paravertebral excision, the question which logically follows is what part, if any, such remaining nerves contribute to the failure of sympathectomy to reduce blood pressure in some patients. Also, it must be recalled that whereas the residual nerves that have been demonstrated as not traversing the sympathetic chains all accompany spinal nerves, there are no somatic nerves to the viscera. Unfortunately, there are no methods for accurate detection of residual sympathetic activity in the splanchnic region as there are for the superficial areas of the body. Working with a series of our patients who had thoracolumbar (T8 - L3) or total sympathectomy Swift and Almy¹⁵ have demonstrated that the abnormal eosinophilic response in the blood stream following the administration of insulin does not differ in these two groups of patients. This suggests that splanchnic denervation is no more complete after total sympathectomy than after the thoracolumbar operation, and that any additional effect of the operation must be attributed to other mechanisms.

The idea seems to be held by many that the advantage of sympathectomy lies in some specific effect on the splanchnic vasculature. Others maintain that whatever advantage the operation possesses is in the de-effarentation of the kidneys or adrenals or both. The added effects of lowering blood pressure after each step of a graded sympathectomy would tend to refute this reasoning, particularly when resections at the extremes of the sympathetic chains,

which should largely affect the extremities, result in lower resting blood pressure and increase in postural hypotension (Figs 1 and 4). Occasionally a bilateral sympathectomy of the lower extremities in a normotensive patient will result in a postural hypotension, and in a small series of patients in whom sympathectomy of all four extremities was performed in rapid succession for Raynaud's disease or hyperhidrosis, postural hypotension of significant degree followed temporarily. The point to be made is that lowering of blood pressure may follow the interruption of any part of the sympathetic system, and whatever part is left functions in the compensatory role of adjustment.

Pharmacologic Evidence—The following two experiments demonstrate by pharmacologic methods that the interruption of residual sympathetic path-

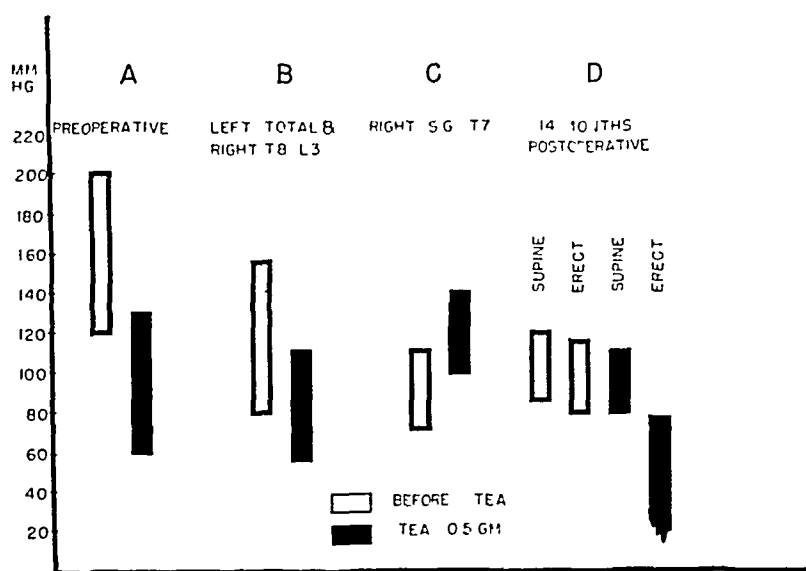


FIG 5—Patient No. 17. Effect of TEA on blood pressure (A) preoperatively, (B) after unilateral total and thoracolumbar sympathectomy, (C) shortly after completion of total sympathectomy, and (D) 14 months later.

ways after total paravertebral sympathectomy results in temporary lowering of blood pressure, but the question of whether residual nerves to the splanchnic region exist is not answered.

Tetraethylammonium chloride (TEA)* has the pharmacologic action of blocking autonomic ganglia. While it has not been found useful in predicting the effect of sympathectomy in hypertensives it does provide a convenient method for demonstrating the presence of residual functioning sympathetics. In seven patients who had total sympathectomy performed in three stages, the administration of TEA between the performance of the second and third stages (that is, when all that remained of the sympathetic chains on both sides was the upper thoracic chain from stellate to T7 on one

* TEA was supplied as Etamon by Parke Davis & Co.

side) always resulted in a significant fall of blood pressure. This apparently indicated the importance of the remaining upper thoracic chain in maintaining the level of blood pressure.

When TEA was given in the early period after completion of total sympathectomy in nine patients there was no appreciable change in blood pressure in two, while in seven there was a definite rise in both systolic and diastolic pressures. This response is interesting but the explanation is not definite. More important is the finding that eight to 14 months later, after postural hypotension was lessened and other evidences of residual sympathetic pathways had appeared, the administration of TEA in three patients was followed in each by a slight fall in resting blood pressure and a marked fall on standing.

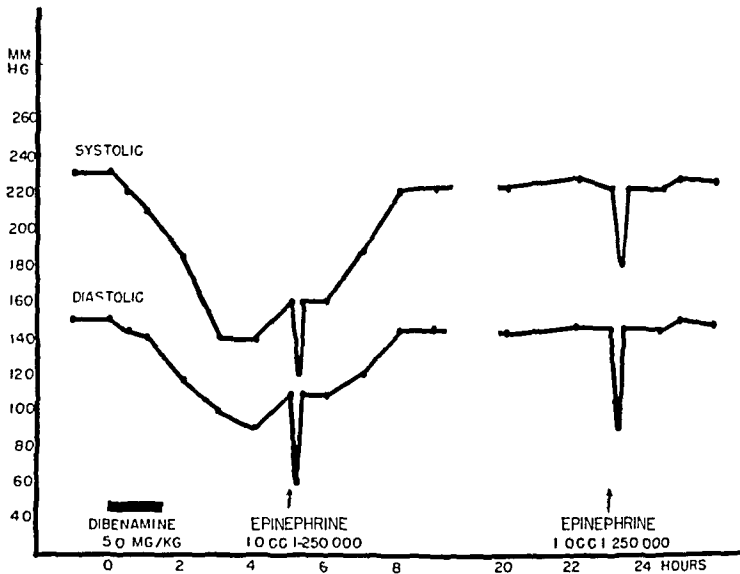


FIG 6—Patient No 8 Effect on blood pressure of dibenamine and "reversal" of epinephrine two years after total sympathectomy

Figure 5 is a graphic record of the effects of TEA at different periods in the course of observation, before, during and after total sympathectomy, in one patient (No 17), and it demonstrates the points that have been made in the use of this drug in showing the relation of residual sympathetic pathways to the maintenance of blood pressure.

Dibenamine* (dibenzyl beta-chloroethylamine hydrochloride) like TEA may cause a fall in blood pressure, but through a different pharmacologic action. It is believed to have a combined effect of producing a sympathetic paralysis of the neuro-effector cells peripherally and of neutralizing epinephrine, that is, its action is both sympatholytic and adrenolytic. Since much has been said about the probable action of vasopressor substances, particularly

* Dibenamine was supplied by Givaudan-Delawanna Inc., Delawanna, N. J., through the courtesy of Dr. W. Gump.

circulating epinephrine, in maintaining blood vessel tone and an elevated blood pressure in some hypertensives, dibenamine seemed an ideal drug for testing the role of epinephrine in a patient (No 8) who had a sustained hypertension two years after total sympathectomy (Fig 6) When dibenamine was given there was a prompt fall in blood pressure, due presumably to the dual action of the drug on residual sympathetic nerves and on circulating epinephrine Before the blood pressure returned to its initial level the administration of epinephrine caused a new fall in blood pressure, which was a reversal of the effect which might have been expected But most important was the observation that 15 hours after return of the blood pressure to its initial level a repeat injection of epinephrine again showed a reversal of the normal reaction From this it is suggested that circulating epinephrine is not the factor that maintains an elevated blood pressure after total sympathectomy, but that residual sympathetic activity or some other unknown factor is

CONCLUDING REMARKS

The justification for employing sympathectomy in the treatment of hypertensive vascular disease still suffers for lack of an understanding of the etiology of the disease, and of the mechanism by which the operation is sometimes beneficial The maintenance of systemic blood pressure is a physiologic mechanism which does not differ basically from other homeostatic mechanisms controlled by the autonomic nervous system Whether essential hypertension is primarily an extreme expression of this function, or whether some other and essentially unrelated factor supervenes, evades many efforts at detection Furthermore, for lack of evidence, there is disagreement concerning the significance or the role of the elevated blood pressure in the disease Sympathectomy has never been anything more than an empirical therapeutic effort, but as such there is ample evidence that it often lowers blood pressure and results in measurable benefits to the patient

For those who are occupied with the performance of the surgery there have been changing ideas regarding the necessity and the safety of increasingly extensive sympathectomy More information was needed on whether complete removal of the paravertebral ganglionated chains would improve on the shortcomings of lesser operations and, just as important, whether the organism could survive this loss without serious limitations The study of the patients of this series has provided some of the answers

The evidence indicates in some measure that there is a quantitative relationship between the extent of the sympathectomy and degree of lowering of the blood pressure This apparently has nothing to do with the more complete or permanent denervation of any specific region such as the splanchnic area, but is related to a more widespread vasomotor paralysis Even so, the percentage of improved results in the blood pressure lowering effect is hardly great enough to justify the somewhat greater morbidity and mortality which

attend the total sympathectomy when compared with a lesser operation such as the thoracolumbar T7 or 8 to L3, and splanchnic nerve resection

There are advantages to the total sympathectomy, however, in that it deafferents and decelerates the heart. It also improves vasospastic states in the extremities which, if not initially present, may become a source of concern after less complete sympathectomy. These effects would seem to constitute the chief, if not the sole, justification for extending the sympathectomy above the mid-thoracic level.

That total paravertebral sympathectomy from the stellate to the third lumbar ganglia does not imply *complete* sympathectomy is impressively established by the evidence of residual sympathetic activity via nerve pathways which do not traverse the ganglionated chains. It is the presence of these residual nerves, augmented in their activity by the demands of the organism to compensate for what has been lost, that maintains some degree of homeostasis and, too, may also compromise the effect of the operation on the level of blood pressure.

It is concluded then, that

1 Total paravertebral sympathectomy from the stellate to the third lumbar ganglia accomplishes a somewhat greater blood pressure lowering effect than does the less extensive thoracolumbar (T7 or 8 to L3 and splanchnic nerve) sympathectomy. However, it does not appear that for this purpose alone there is enough advantage to the former to justify its use except in special circumstances.

2 The special circumstances include chiefly, angina pectoris, tachycardia and vasospastic states in the extremities. In these conditions total sympathectomy has demonstrated its worth.

3 Homeostasis has not been significantly threatened by the operation, and after a period of readjustment patients are able to lead relatively normal lives within the limits of extreme demands on the body.

4 Much of the preserved homeostasis, as well as other evidences of persistent sympathetic activity after total sympathectomy, is believed due to the existence and augmented activity of sympathetic nerves that are not interrupted by the operation.

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DISCUSSION—DR REGINALD H SMITHWICK, Boston, Mass I think Dr Ray and I agree pretty completely on most aspects of the surgical treatment of hypertension I would like to state my feelings about total sympathectomies as briefly as possible

In investigating the problem of hypertensive cardiovascular disease and its treatment by sympathectomy, it has been my policy to commence with the least extensive procedure which might be helpful and, having evaluated the result, then to extend the maneuver if nothing worthwhile seemed to have been accomplished

Having observed the response to subdiaphragmatic or supradiaphragmatic splanchnicectomy in groups of patients, the operation was extended in failures to a combined maneuver by reoperating upon the same individuals and increasing the extent of the maneuver either upward or downward Because it was possible to increase the percentage of early successes by about 30 per cent without adding unduly to the morbidity or mortality, the combined procedure, called lumbodorsal or thoraco-lumbar splanchnicectomy, was adopted as a standard procedure a little over ten years ago

In approaching the question of total sympathectomy the same plan has been used, namely, to extend the operation in failures following thoracolumbar sympathectomy to total sympathectomy in subsequent stages Over a period of 12 years I have performed total sympathectomy in 16 patients I have not been impressed by any additional benefit to the patients either with regard to blood pressure levels or the further abolition of reflex vasomotor elevations of blood pressure as judged by the Valsalva maneuver

I have been impressed by the fact that four of the 16 totally sympathectomized patients were totally disabled for long periods of time because of their inability to stand, having lost both their capacity to constrict the splanchnic bed and to accelerate the heart rate This is demonstrated by the first slide

It is my belief that total sympathectomy should never be performed as a primary procedure in hypertensive patients The morbidity and mortality will be too great, aside from the probability that it is unnecessary Also, the success or failure of surgery

of this sort depends upon many factors other than the extent of operation—particularly the amount of cardiovascular damage which exists at the time of operation

My experiences with thoracolumbar splanchnicectomy have led me to believe that there are two groups of patients who should not be treated in this fashion, namely, those with coronary heart disease and angina pectoris, and those with postural tachycardia. These, I feel, are best treated by a transthoracic sympathectomy, removing the chains bilaterally from the inferior cervical to the twelfth thoracic ganglia in the former, and from the second thoracic to the twelfth ganglia in the latter group. These operations are performed at present in about 15 per cent of the patients, and with thoracolumbar procedure in about 85 per cent of patients.

I personally do not feel that it is necessary to do a total sympathectomy as a primary procedure in patients with hypertension and angina pectoris or tachycardia.

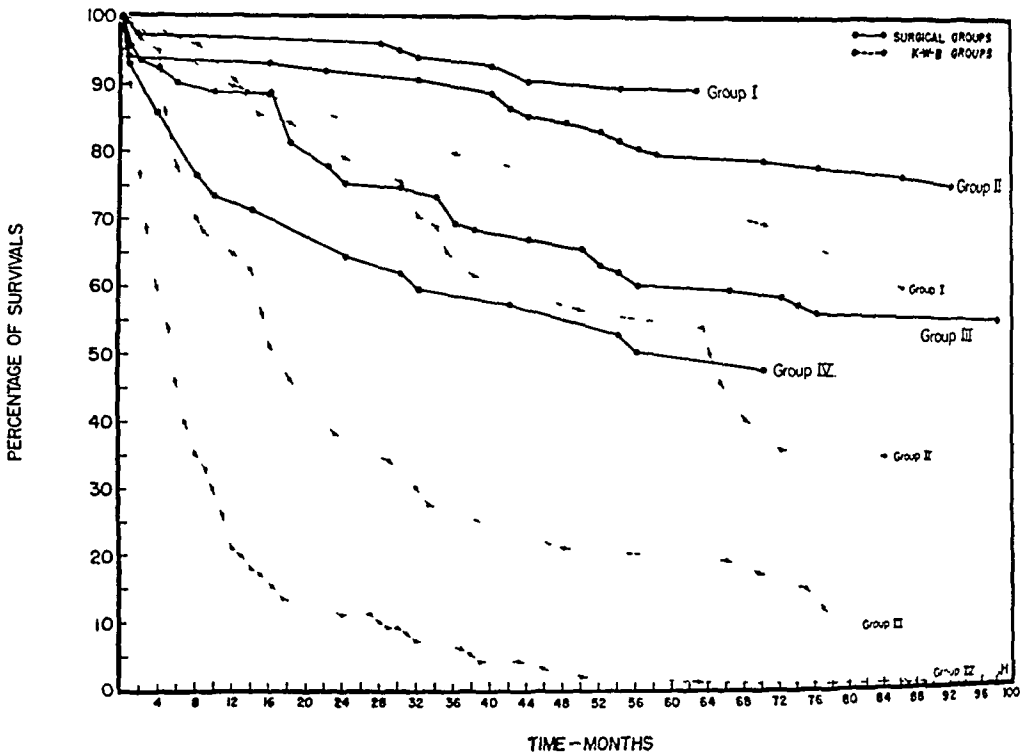


FIG 1—Survival curves following lumbodorsal splanchnicectomy, 299 cases followed five to nine years arranged according to Keith, Wagener and Barker Groups and compared with their 219 cases followed five to nine years

I should like to say a word about the value of splanchnicectomy in the management of hypertensive cardiovascular disease. This, in the last analysis, will be judged by its effect on the progress of cardiovascular disease and upon life expectancy. We now have a sufficient number of consecutive, unselected cases followed for a sufficient length of time after lumbodorsal splanchnicectomy to indicate that the progress of cardiovascular disease has been slowed, and life expectancy increased to a statistically significant degree.

This is indicated by a comparison of the survival curves of our patients with those of Keith, Wagner and Barker, of the Mayo Clinic. Their data for medically treated patients, published in 1939, stands today as the best available standard by which to judge the efficacy of any form of treatment for hypertensive cardiovascular disease.

The illustration shows the survival curves of Keith, Wagner and Barker for a group of 219 unselected hypertensive patients divided into four groups according to the severity

of the changes in the eyeground. There are minimal vascular changes in Group 1, sclerotic changes in Group 2, hemorrhage or exudate and vascular changes in Group 3, and the so-called malignant hypertensives in Group 4, patients who generally have hemorrhage and exudate and always papilledema. The percentage of survivals that you see depends upon the severity of the disorder at the time of the beginning of the period of observation, and particularly, in Groups 3 and 4, by the end of about seven years all of the patients are dead.

The figure also shows our survival curves for the first 299 consecutive unselected cases which were treated by thoracolumbar splanchnicectomy, and divided into comparable groups. The difference between the two series is very striking. It is highly significant on statistical analysis for Groups 2, 3 and 4.

It is my belief that if one performs the right type of operation at the proper stage of the disorder, surgery is of real value in the management of this disease. This would exclude the use of total sympathectomy as a primary procedure and the use of surgery of any sort in the terminal or near terminal stage of the disease.

THE USE OF BACITRACIN IN EXPERIMENTAL *CLOSTRIDIUM WELCHII* INFECTION IN GUINEA PIGS*

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THE LABORATORY EXPERIMENTS reported in this paper were conducted to determine the value of the antibiotic, bacitracin, as a prophylactic agent against *Clostridium welchii* infection in guinea pigs

In May, 1943, while studying the bacterial flora of badly contaminated civilian accidental wounds, Johnson, Anker and Meleney discovered an organism which produced a powerful antibiotic agent¹ The organism is a gram-positive, spore-forming aerobic rod and it belongs to the *Bacillus subtilis* group The antibiotic has been named bacitracin It possesses a wide range of antibacterial activity It is effective, in vitro, against gram-positive organisms such as streptococci, pneumococci, staphylococci, micrococci corynebacteria and clostridia, and against two species of gram-negative organisms, gonococci and meningococci It is ineffective against gram-negative aerobic rods such as members of the coliform, proteus, and pyocyanous groups Spirochetes are highly susceptible, but fungi, such as monilia and cryptococci, are resistant

Johnson, Anker, Scudi and Goldberg² reported the first observations on the use of bacitracin in clostridial infections in animals Guinea pigs were protected against the development of gas gangrene when *Clostridium welchii* or *Clostridium septicum* was the infecting organism Eighty to 90 per cent of the animals survived when an 18-hour culture of *Clostridium welchii* was injected into the thigh muscles in the amounts of 0.5 to 0.25 cc and bacitracin was injected immediately subcutaneously, followed by subsequent doses every 3 hours for 36 to 72 hours The first dose was 400 units, the second dose 200 units and the remaining doses 100 units Some swelling of the leg occurred in the treated animals, but after 12 to 18 hours this subsided completely All of the untreated control animals died within 24 hours When a similar dosage of bacitracin was given after a 3-hour delay between contamination and the first treatment with bacitracin, the animals were not protected

Similar studies with bacitracin in experimental clostridial infection have been conducted by Altemeier³ Animal wounds containing crushed muscle and sterile dirt were contaminated with one M L D of *Clostridium welchii* The animals were treated with 2000 or 8000 units of bacitracin per kilogram daily, divided into doses given at 4-hour intervals The result of this experi-

ment showed that bacitracin had a definite prophylactic and therapeutic effect on these infections

METHODS

In a previous communication⁴ it was pointed out that it was highly desirable to devise experiments in which clostridial infections in animals simulate as closely as possible clinical gas gangrene in human beings. In the experiments which are to be described in detail, wounds were produced in anesthetized guinea pigs and contaminated with *Clostridium welchii* which is the organism most frequently associated with clinical clostridial infections in human beings. The study was conducted so that in each experiment one group of animals received a wound and a contaminating inoculum, but was given no bacitracin and the animals serving as controls, while another group of animals comparable in number and in weight received a wound, an identical contaminating inoculum, and bacitracin. In principle the method used to produce the experimental lesion is that described in 1940 by Legroux.⁵ The object of this investigation was to produce in guinea pigs lesions simulating war wounds contaminated with clostridia and to treat them with chemotherapeutic agents.

In the study herein reported guinea pigs were used as the experimental animals. Their weights ranged from 294 to 1038 grams, however, the usual weight in any given experiment ranged from 325 to 550 Gm. The hair was removed from both hindquarters by clipping. The animals were anesthetized with sodium pentobarbital administered subcutaneously in the form of a 1 per cent solution in distilled water. Three and one-half to 4 cc of this solution per kilogram of body weight produced satisfactory anesthesia. The skin of one hindquarter and leg was scrubbed with a brush, using soap with an added chemical^{*} and water, after which this area was sprayed with an antiseptic solution.[†] The operation was performed under aseptic technic. A skin incision 1 cm in length was made over the gluteus maximus muscle of the animal. After this muscle was exposed, a portion of it was traumatized by crushing with a Kocher clamp. An effort was made to achieve uniformity in the size of the incision and the degree of trauma. The skin wound was then closed with non-absorbable suture material and covered with collodion, which was allowed to dry. The latter two steps were performed to reduce the probability of secondary contamination of the operative wound, to prevent loss of the bacterial inoculum, and to insure an anaerobic environment in which the organisms could multiply. Finally the wound was contaminated by injection of bacteria through the adjacent normal skin into the traumatized muscle, using a hypodermic needle and syringe.

Actively growing vegetative forms of *Clostridium welchii* cultured in cooked beef heart medium were used in the dosage recorded below to contaminate

* Bis-(3,5,6-trichloro-2-hydroxyphenyl)methane

† Formula: HgCl₂ 0.7 Gm, tricresol 5 cc, acetone 100 cc, alcohol (95%) 525 cc, water 375 cc

‡ The organism used was obtained from Dr. Frank L. McIneny, of New York, who had originally obtained it from Dr. Ivan C. Hall. It is identified as Strain 1029.

nate the wounds. Before each experiment a gram-stained smear of the culture was made for the purpose of determining the purity of the culture. At the same time a serial dilution of a portion of the culture was made to determine the highest dilution in which the organism could be grown. This value for the 33 separate experiments was as follows: 10^4 in 2 experiments, 10^7 in 2, 10^9 in 12, 10^{10} in 9, 10^{11} in 5, and 10^{12} in 3.

In one experiment in which 0.1 cc. of a 12-hour culture was used, only four out of 11 control animals died of clostridial infection, however, all six of those that survived the 15-day period of observation showed evidence of clostridial

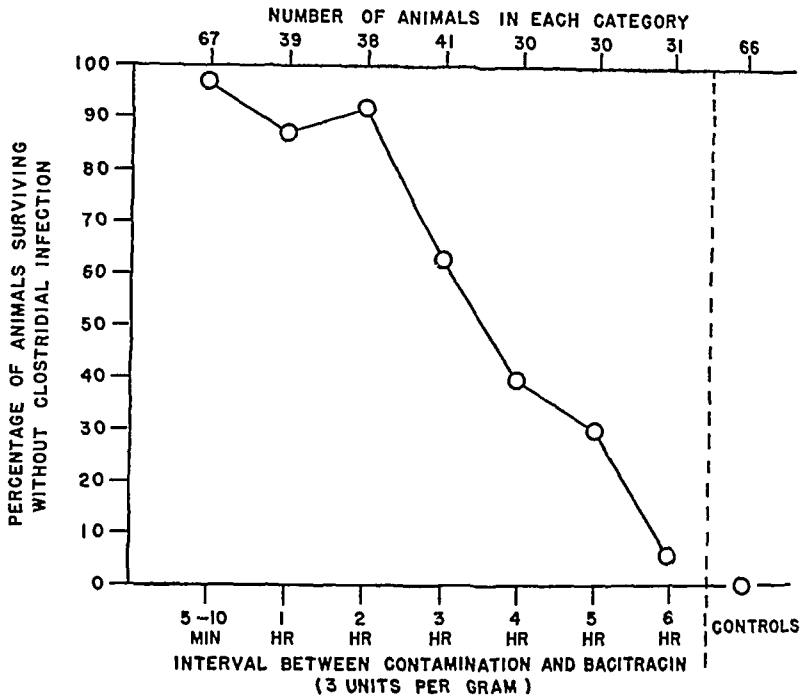


FIG 1—A graph to show the percentage of animals surviving for 15 days without evidence of clostridial infection in those experiments (See Table III) in which the administration of bacitracin was delayed for varying intervals of time following wound contamination. The contaminating inoculum consisted of 0.1 cc. of a 4 to 6½ hour culture of *Clostridium welchii*. Bacitracin (Lot No B480420) in the amount of 3 units per gram was given to one group of animals. Another group served as controls.

infection. After this experiment the inoculum was increased to 0.2 cc. and in four experiments performed with this inoculum 20 out of 33 control animals died of clostridial infection. Of the 13 animals that survived the 15-day period of observation all showed evidence of clostridial infection. Because of dissatisfaction with the results of these early experiments, the inoculum was further altered, and in the remaining experiments a 4 to 6½ hour culture was used and 0.1 cc. was administered. The results became highly satisfactory and among 180 control animals 173 died of clostridial infection. Of the 173 animals 88 per cent died within 72 hours of the contamination. All of the seven animals

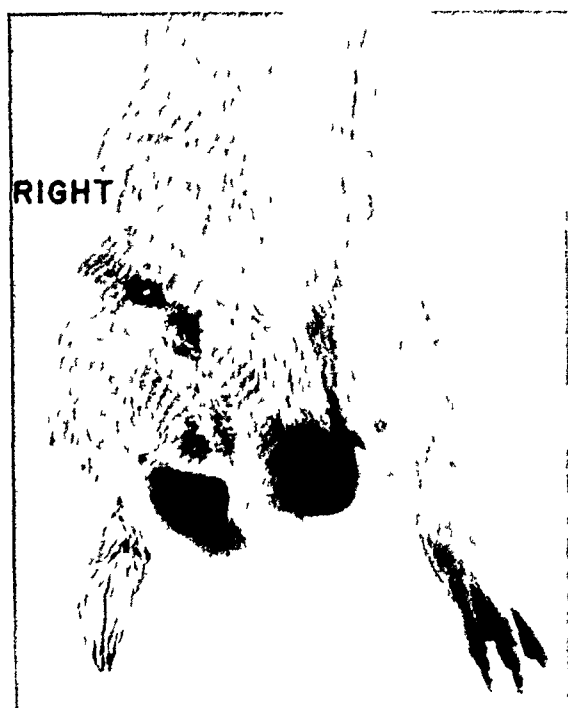


FIG 2



FIG 3

FIG 2—Photograph of a control animal taken shortly after death 20 hours following wounding and contaminating with 0.1 cc of a culture of *Clostridium welchii*. Note the extensive edema and discoloration of the right thigh, groin and lower portion of abdomen.

FIG 3—Photograph of an animal wounded and contaminated at the same time as the one in Figure 2, but one that received bacitracin in the amount of 2 units per gram shortly after contamination. Note normal appearance of the wounded right leg. This animal survived the 15-day period of observation.

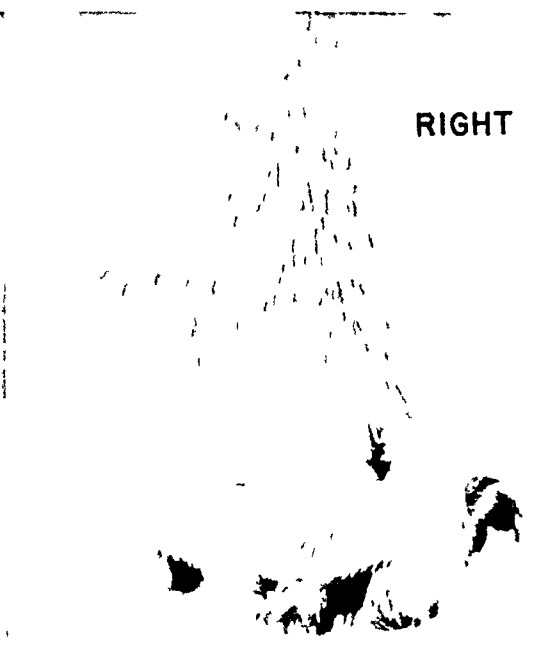


FIG 4—Photographs (anterior and posterior views) of an animal that was given bacitracin in the amount of one unit per gram shortly after receiving a wound contaminated with *Clostridium welchii*. This animal survived 17 days at which time he was photographed, sacrificed and autopsied. There was no evidence of clostridial infection. Note the small crust covering an otherwise cleanly healed wound.

that survived the 15-day period of observation showed evidence of clostridial infection. A mortality rate of this magnitude obviously offers an adequate challenge to the antibiotic.

Bacitracin* was dissolved in physiologic saline solution and administered intramuscularly in varying dosages. The dosage was calculated on the basis of the weight of the animal, and in this report is expressed in units per gram.

In three groups of experiments the antibiotic agent was given 5 to 10 minutes after contamination of the wound except in one experiment in which the



FIG 5—Photographs (anterior and posterior views) of an animal that was given bacitracin in the amount of 3 units per gram shortly after receiving a wound contaminated with *Clostridium welchii*. This animal survived 17 days at which time it was photographed, sacrificed and autopsied. Note the completely healed operative wound. (The hairless area in the photograph on the right.)

interval was 20 minutes. The amount of drug administered in the different experiments varied, ranging as follows: 166 units per Gm every 4 hours until 18 injections had been given, 33 units per Gm every 4 hours until 3 injections had been given, and finally single injections in amounts of $\frac{1}{2}$, 1, 2, 3 and 10 units per Gm.

In a fourth group of experiments the administration of bacitracin was delayed following contamination of the wound but the dosage was kept at a constant of 3 units per gram. The interval between contamination and administration of the drug ranged from 5 to 10 minutes up to 6 hours.

During the postoperative period each animal was kept in a separate cage and offered a diet consisting of commercially prepared food pellets, fresh vegetables and water. The animals were observed at frequent intervals and notes were made concerning their general state of health and the appearance of the local

* The bacitracin used in these experiments was supplied by Commercial Solvents Corporation of Terre Haute, Indiana.

lesion Every animal that died was subjected to a postmortem examination, and cultures were obtained from the tissue exudate in almost all of those that showed gross evidence of infection All surviving animals were kept under observation for 15 days

RESULTS

When infection occurred following wound contamination the clinical course of the guinea pigs and the gross pathologic lesions were characteristic The animal developed swelling in the region of the wound which promptly spread, so that the ipsilateral thigh was soon included Usually before the animal died the process involved the groin and the abdominal wall, and in some instances the thoracic and even the cervical regions The swelling became noticeable in the region of the wound and in the wounded leg in approximately 12 hours and often reached the abdominal or thoracic walls within 18 to 24 hours Most of the animals that survived infection for as long as 72 hours developed skin necrosis in the area immediately surrounding the site of operation In some this necrosis was even more widespread, involving areas on the leg, groin or abdominal wall The infected animals looked ill They were listless, inactive, and ate poorly These signs progressed with the passage of time At postmortem examination, made in all fatal cases, in the area immediately surrounding the wound, the muscle was invariably pale, avascular and necrotic, and often liquefied Beyond this zone there were hemorrhagic congestion and edema of the muscle In the adjacent subcutaneous tissue spaces there was an exudate more often serosanguineous, but occasionally slightly gelatinous This was often extensive, and seemed to accumulate in pockets in association with gas Cultures taken from this exudate consistently yielded *Clostridium welchii* Every control animal developed the lesions of clostridial infection, however, some recovered despite the fact that the process ultimately reached an advanced stage These animals showed during the 15-day period of observation the same type of swelling as those which died and showed also subsequent spontaneous wound disruption, with the discharge of foul-smelling purulent material and finally, ulceration and crust formation When sacrificed and autopsied, there

RIGHT



FIG 6—Photograph of a control animal 14 days after wounding and contamination with *Clostridium welchii* Note the extensive amount of crust, ulceration and gangrene This is one of a small number of control animals that survived the 15-day period of observation It showed evidence of clostridial infection at autopsy

were varying degrees of muscle injury ranging from complete dissolution to slight superficial necrosis. Figure 6 is an illustration of such an animal.

In the majority of the animals that did not develop active infection there was primary healing of the wound. In a few instances the operative wound became superficially ulcerated, but in no way showed any of the characteristics of clostridial infection. Some animals among those receiving bacitracin showed local reactions which took the form of swelling involving the ipsilateral leg or even the abdominal or thoracic walls. This usually appeared by the end of the first 18 to 36 hours after operation and gradually subsided within the next 24 to 48 hours. This reaction apparently did not result in permanent change. When the period of observation had terminated these animals were sacrificed and autopsied, and in every instance the region previously the site of swelling appeared to be entirely normal. Other animals in the bacitracin group survived

TABLE I—Results of the first five experiments in which there was a high survival rate among control animals and a loss of numerous bacitracin animals due to causes other than clostridial infection. In these experiments the contaminating inoculum consisted of either 0.1 or 0.2 cc of a 12-hour culture of *Clostridium welchii*. Bacitracin (Lot No. B471231S) was administered as indicated above.

	Bacitracin				Controls
	1.66	3.3	10	5	
Units per Gm. in each injection	1.66	3.3	10	5	
Number of injections	18*	3*	1	1	
Total dosage of bacitracin in units	30	10	10	5	
Total number of animals	19	44	15	15	44
Survived without evidence of clostridial infection	5	37	12	14	0
Died of causes other than clostridial infection	14	7	3	1	0
Survived but showed clostridial infection	0	0	0	0	20
Died of clostridial infection	0	0	0	0	24

*First injection 5-10 minutes after wound contamination, subsequent injections every 4 hours.

the 15-day period of observation, but showed, as is described above, changes compatible with clostridial infection. All such examples occurred among those animals receiving 2 units or less of bacitracin per gram at the time of contamination or among those receiving 3 units per gram given after the lapse of an interval of time.

A total of 747 guinea pigs was used in this study. Thirty-three separate experiments were performed, each involving from four to 38 animals. The results of these experiments are recorded in Tables I, II, and III. These tables are based on observations made on 724 animals, 23 animals having been excluded from consideration. Each of the animals excluded had been anesthetized, operated upon, and the wound had been contaminated, but each died within the first 12 postoperative hours, never having recovered from anesthesia. The exclusion of such animals seems justified, since none had developed clinical evidences of clostridial infection by the time of death.

In the first five experiments (Table I) the mortality rate among the control animals was too low to offer a sufficiently critical test for the antibiotic agent. Moreover, a large number of the animals treated with bacitracin died of

causes other than clostridial infection. Therefore no conclusion can be drawn from this group of experiments.

The results in the remainder of the experiments are decidedly more conclusive. Those experiments in which bacitracin was given shortly after wound

TABLE II—*Results of experiments in which bacitracin (Lot No B480420) was administered between 5 and 10 minutes after wound contamination. The contaminating inoculum consisted of 0.1 cc of a 4 to 6½ hour culture of Clostridium welchii. The controls received a contaminating inoculum but no bacitracin.*

	Bacitracin Amounts in units per gram				Controls
	3 Units	2 Units	1 Unit	0.5 Unit	
Total number of animals	51	22	33	25	114
Survived without evidence of clostridial infection	50 (98%)	19 (86%)	25 (75%)	6 (24%)	0 (0%)
Died of causes other than clostridial infection	0	1	3	2	0
Survived but showed clostridial infection	0	0	4	7	2
Died of clostridial infection	1	2	1	10	112

contamination are summarized in Table II. From this table it can be seen that among 114 control animals every one developed clostridial infection and only two survived the 15-day period of observation. When bacitracin in the amount of 3 units per gram of the animal's body weight was given to 51 animals, 98 per cent showed no evidence of clostridial infection and survived. When smaller

TABLE III—*Results of experiments in which varying intervals of time were allowed to lapse between wound contamination and the administration of bacitracin. The contaminating inoculum consisted of 0.1 cc of a 4 to 6½ hour culture of Clostridium welchii. Bacitracin (Lot No B480420) in the amount of 3 units per Gm was given to one group of animals. The remainder served as controls.*

	Interval between wound contamination and administration of bacitracin							Controls
	5 to 10 Minutes	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours	
Total number of animals	67	39	38	41	30	30	31	66
Survived without evidence of clostridial infection	65 (97%)	34 (87%)	35 (92%)	26 (63%)	12 (40%)	9 (30%)	2 (6%)	0 (0%)
Died of causes other than clostridial infection	2	4	0	1	1	0	0	0
Survived but showed clostridial infection	0	1	1	3	7	4	2	5
Died of clostridial infection	0	0	2	11	10	17	27	61

amounts of the agent were given the figure for survival without evidence of clostridial infection decreased, being 86 per cent, 75 per cent and 24 per cent for 2, 1 and ½ units respectively.

The experiments in which an interval of time was allowed to lapse between drug administration and wound contamination (Table III and Figure 1) clearly demonstrate that delay in administration of the drug beyond two hours significantly reduces its effectiveness.

DISCUSSION

Although the clostridial infection produced by the method herein described simulates clinical gas gangrene in human beings, it is not identical with it. There are a number of differences. The contamination in these experiments was undoubtedly proportionately more massive than that usually occurring in traumatic wounds in human beings. Moreover, the organisms entered the wound in an actively multiplying state, whereas in the usual clinical wound the contaminating clostridia enter in the spore form. Thus, for comparable intervals following contamination, the experimental lesion is apt to be further advanced bacteriologically than is the clinical wound. Gas gangrene in the human being is usually polymicrobial whereas in these experiments only one organism was used. In the mixed flora of the clinical case there may be organisms which produce substances that inactivate an antibiotic otherwise effective against the clostridial flora of the wound. This may be one element in the explanation of the efficiency of penicillin in certain cases of clostridial infection and its relative ineffectiveness in others.⁶ With but one known exception,⁷ the action of bacitracin is not influenced by the products of bacterial metabolism.

The usefulness of bacitracin is limited by evidences of toxicity which have been reported.^{8,12} Thirty-nine out of 500 animals receiving bacitracin in the study herein reported died of causes other than clostridial infection. These animals either had diarrhea during life or showed pneumonia at autopsy. There appear to be at least two possible explanations. (1) These processes are primary conditions and represent intercurrent infections, or (2) They are secondary terminal manifestations of a primary process which may be some form of drug toxicity. In favor of the former explanation is the fact that during the period in which this high mortality rate was occurring a great many animals in the stock guinea pig colony were also found dead. Unfortunately these were not autopsied and there is no explanation for the causes of their deaths. Moreover, the susceptibility of guinea pigs to intercurrent infections is well known. In favor of the second explanation, namely, that the deaths were due to drug toxicity, is the fact that the mortality rate closely parallels the total amount of bacitracin administered. It is noteworthy that observations^{11,13} have been made which indicate that Lot B451231S of bacitracin is more toxic than Lot B480420.

Renal changes have been reported^{8,9} in laboratory animals receiving bacitracin. In view of this observation, kidney tissue has been saved from a number of the animals that died of causes other than clostridial infection. Microscopic study revealed that many of those that received bacitracin in the total amount of 30 units per gram showed necrosis of the epithelium of the convoluted tubules.

There is hope that the disadvantage of toxicity may be overcome, and if it is, a potent agent will be added to the ever increasing antibiotic armamentarium against surgical infections. At the present time adequate and early surgical debridement is the most effective means of prophylaxis, and early diagnosis and

prompt surgical extirpation of the diseased tissues the most effective therapy for clinical gas gangrene. Other measures, such as antitoxin, transfusion and chemotherapy are useful and necessary adjuncts, but in the search for the ideal chemotherapeutic agent with which to combat clostridial contamination and infection one must not lose sight of the fact that surgery remains our most effective weapon.

SUMMARY AND CONCLUSIONS

Experiments were conducted in which wounds were produced in anesthetized guinea pigs and contaminated with *Clostridium welchii*. Untreated control animals developed lesions simulating clinical gas gangrene in human beings.

Bacitracin, an antibiotic derived from a gram-positive spore-forming rod of the *Bacillus subtilis* group, was used as a prophylactic agent and administered intramuscularly.

The first five experiments involving 137 animals gave inconclusive results because of a high survival rate among control animals and a loss of numerous treated animals due to causes other than clostridial infection.

In subsequent experiments involving 245 animals there were 114 control animals of which all but two died of clostridial infection. Among 51 animals that received bacitracin in the amount of 3 units per gram, shortly after wound contamination, 98 per cent showed no clostridial infection and survived the 15-day period of observation. Amounts less than 3 units were less effective.

Experiments involving 342 animals in which the bacitracin dosage was 3 units per gram administered at varying intervals following wound contamination, showed that delay in administration of the drug beyond 2 hours significantly reduces its effectiveness.

These experiments indicate that 3 units per gram of body weight is an effective dose of bacitracin, and when administered at the time of wound contamination is capable of protecting guinea pigs against *Clostridium welchii* infection. When the interval between contamination and drug administration is lengthened beyond 2 hours the prophylactic effectiveness of the drug diminishes with each hour and is completely lost by 6 hours. Due to differences between the infection in the experimental animal and the human being, these results must be applied with caution to the clinical problem. However, they do suggest that when bacitracin becomes available in a form which can be given with safety it may be a valuable adjunct to other well recognized forms of treatment in clinical gas gangrene in the human being.

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DISCUSSION—DR EDWIN P LEHMAN, Charlottesville, Va I have been greatly interested in following this work with bacitracin There is no question of the fact that these observations have proved its efficacy as a prophylactic in experimental *Clostridium welchii* infection in the animal

I should like to re-emphasize the point that Dr Sandusky has made, namely, that, up to the present time, at least, any antibiotic therapy, including bacitracin, must be considered solely as an adjunct to surgical treatment in accordance with established principles Even such striking results as those just presented do not indicate the use of bacitracin instead of surgery This point must be stressed repeatedly in teaching, although of course it does not need stating before this audience

Furthermore, it should be repeated that the present status of preparation of this substance does not yet permit its general use by systemic administration in the prevention or treatment of human *Clostridium welchii* infection There is reason to predict that it would prove as effective in the human being as in the animal if it were permissible to use it

At the present time the problem of its toxicity is under intensive study, and it now seems possible to get batches of the drug which show little or no toxicity Until the toxic factor can be reduced consistently or eliminated during the preparation of bacitracin, the latter cannot be made generally available for systemic use, although it has been released for local administration in human beings

I should like to emphasize also one other point in regard to bacitracin which Dr Sandusky did not have time to make Bacitracin has been shown by others to be inactivated by the products of bacterial metabolism in the case of only one known organism In this respect it differs from penicillin, which is so frequently inactivated by penicillinase When it becomes permissible to use it in the clinical case it should therefore theoretically be effective when the infection is one of *Clostridium welchii* with variously mixed other flora, as in the usual case of human gas gangrene

Dr Sandusky is continuing work with bacitracin using other organisms of the clostridial group He also has started studying aureomycin and chloromycetin Results with aureomycin in preliminary experiments in animals, using the same technic as he has described, are encouraging He has found that chloromycetin is effective in vitro against the clostridia The animal experiments have not been sufficient in number to allow any pre

diction about the effectiveness of chloromycetin against *Clostridium welchii* in the living organism

DR. FRANK L. MELNBY, New York, N. Y. When I looked over the program of the meeting, I was particularly impressed with the fact that only two of the papers have to do with infections. This shows perhaps how far we have come in recent years in bringing infection under control.

But there are still a few problems of infection which have not yet been solved, and I believe that gas gangrene is one of them. Those who saw gas gangrene during the war (and I believe Dr. DeBakey can give us the figures) realize that the problem of gas gangrene was not solved by penicillin or the sulfonamides.

I have not seen a case of gas gangrene in the last two years, probably because our hospital has no ambulance service, and particularly avoids the admission of street accidents, including gunshot wounds and compound fractures in which gas gangrene is so prone to develop. However, if we have another war, which God forbid, gas gangrene will be a major problem among the victims of atomic bombs, and until we have peace established we must prepare for that eventuality.

I am glad that Dr. Sandusky has been able to continue his studies on experimental gas gangrene, so well begun before the war, when he was trying to evaluate the sulfonamides in the treatment of this disease. These experiments which he has done recently seem to indicate that bacitracin can prevent the development of this disease in guinea pigs if given in time and in sufficient quantities. They suggest that it may be a valuable adjunct to the accepted forms of treatment in clinical gas gangrene in human beings.

The question arises as to whether the presently available bacitracin is safe to use in large enough doses to be effective. That is the feature of Dr. Sandusky's paper that I wish to discuss.

It was thought that bacitracin might be worthy of consideration for Dr. Sandusky's studies in the treatment of gas gangrene when we studied its antibacterial spectrum and found that it was active against a wide variety of organisms, and was particularly active against the gas gangrene group. Furthermore, it was not inactivated by the organisms which inactivate penicillin by the production of penicillinase, and which are so common as secondary factors in cases of gas gangrene.

(Slide) This is a chart showing the spectrum of bacitracin. You will see that it is effective against a large group of organisms, staphylococci, streptococci, pneumococci, gonococci, meningococci, diphtheria bacilli, and so on. It is not effective against many of the aerobic gram-negative rods, but it is effective against all of the gas gangrene clostridia and tetanus and also the anaerobic streptococci. These organisms are the ones that are to be considered as the essential causes of gas gangrene, with many secondary contaminants among the other bacterial groups. I wish to remind you also that bacitracin has significant synergistic action with penicillin in the inhibition of growth and the death of the gas gangrene organisms as well as other bacteria.

Some of you may remember that at the meeting of the American Surgical Association a year ago I reported on 105 cases of surgical infection treated systemically with bacitracin, and I brought up the fact that while we had found it effective in controlling many types of infection, we were beginning to run into cases which showed a considerable degree of kidney irritation. This was true particularly in cases treated in the spring of 1948, when we began to use material made by the deep tank growth of the organism, and which was inconsequential when we employed the earlier preparations made by surface growth.

We have now treated over 225 cases, and they can be divided into three groups. The first 75 patients were treated with the Ben Venue Laboratories product grown on surface culture and they showed very little evidence of nephrotoxicity. The next 75 patients were treated with the first product of the Commercial Solvents Company made in the deep

tanks, and some cases showed rather alarming albuminuria, and a rise in retained non protein nitrogen, and in a few cases we were required to stop treatment for fear of serious kidney damage. The last 75 patients were treated with selected lots of the Commercial Solvents Company's product, and with these we have again had very little trouble. So, that now we have regained our confidence in the safety of the systemic administration of this antibiotic although, for the present, it is wise to limit the dosage to 400 units every six hours per kilo of body weight.

After we had run into difficulties with the second group of cases, we took stock of our results and found that the toxicity was largely confined to certain lots. This is shown in the next slide.

(Slide) These are the lots made by the deep tank method. We had only one case of severe toxicity with the surface growth bacitracin. In that case, we had to stop treatment because of nausea and vomiting and albuminuria, but they promptly cleared up following cessation of treatment. However, with the deep tank lots, we made a careful study of the clinical evidences of kidney irritation. These results are divided into three groups—cases showing none or only slight and transient evidences, those with moderate but transient evidences, and those which we called severe because of nausea and vomiting or a degree of albuminuria, casts, or cells in the sediment, or a rise in N P N, which made us fear that the kidneys might be damaged. There were no fatalities, however, that could definitely be ascribed to bacitracin in any patients in this severe group. In this study we also noted those patients which had some evidence of kidney damage, probably due to the infection itself.

As a result of this study, since July 1, 1948, up to February 15, 1949, we have treated all of our cases except six with lots which have shown, by the Food and Drugs Administration test, an LD 50 of 500 units for a 20-Gm mouse. The F D A tests are shown on the slide, and have been correlated with the clinical results. You see here six cases treated with two lots which were more toxic according to that test, and these gave us a little

Degree of Toxicity According to Lot Numbers Used in the Systemic Administration of Bacitracin Prepared by the Deep Tank Method

Lot Number	F D A LD 50-20 Gm Mouse	Number of Cases*	Daily Dosage	Some Evi- dence of Kidney Damage Before Rx	Toxicity with Treatment		
					None or Slight Transient†	Moderate Transient‡	Disturb- ing§
January to June 1948							
C S 471212S	287 ±18	19	40-260 000	9	2	8	9
C S 471217S	255 ±20	5	88-260 000	2	0	4	1
C S 471231S	240 ±21	8	40-280 000	3	1	5	2
C S 480114S	283 ±18	15	40-196 000	6	5	8	2
C S 480120S	361 ±23	14	14-200 000	4	9	4	
C S 480210S	262 ±17 7	10	16-160 000	3	2	2	6
C S 480212S	224 ±15 2	7	50-188 000	5	0	2	5
C S 480218S	500 or less	7	40-200 000	1	5	1	1
July 1948 to February 15, 1949							
C S 480420	500	37	2-120 000	15	20	16	1
C S 480408	500	9	40-80 000	5	6	3	0
C S 4 0512	322 ±26 8	4	40-50 000	0	0	1	3
C S 480520	435 ±80 9	2	10-40 000	0	0	1	1
C S 480616	about 500	10	2-80 000	5	6	4	0

* A few cases were treated with more than one lot and are included with each lot used.

† Albumin one plus occasional granular cast, a few white cells and epithelial cells.

‡ Albumin 2-3 plus a few to moderate granular casts, white cells, epithelial cells. Treatment not interrupted.

§ Albumin 4 plus moderate to many granular casts, white cells, epithelial cells and few to moderate red cells or nausea and vomiting or significant rise in retained nitrogen. Considered advisable to stop treatment.

trouble. However, with five lots meeting this specification, the evidences of severe kidney irritation were minimal.

It is true that we have used somewhat smaller doses during this period also for fear of kidney irritation, but with the two lots of higher toxicity with which we got into difficulties, we used the same doses as with the less toxic lots and as soon as we stopped the former and treated these same cases with the latter lots, the difficulty disappeared. Therefore, with our experience with the last 75 cases we have developed an increasing confidence in the safety of this agent and if the manufacturers can meet this specification we believe that it can be more generally employed.

I do not wish anyone any hard luck, but I hope that I soon will have the opportunity of using bacitracin in the treatment of clinical gas gangrene. I shall use it in the next case I see, but I shall use it as an adjunct to surgery and antitoxin and such other methods of treatment as are indicated by the case in hand.

DR WILLIAM R. SANDUSKY, Charlottesville, Va. Dr. Meleney has just pointed out that the degree of toxicity among different commercial lots of bacitracin varies. Observations which we have made substantiate this point. We have used bacitracin in guinea pigs other than in the study just reported. In some it was administered in connection with experiments in which *Clostridium novyi* was the contaminating organism and in others bacitracin alone was given for the purpose of comparing two different commercial lots of the drug. Altogether bacitracin has been administered to 726 animals. Among this number there were 99 deaths due to causes other than clostridial infection. That drug toxicity is a possible cause of these deaths has already been discussed. The following table presents an analysis of these deaths in relation to varying dosages of two different commercial lots of the drug. It demonstrates that for the larger dosages there is a significant difference in the mortality rates between the two different commercial lots of bacitracin.

In closing, I should like to thank Dr. Lehman and Dr. Meleney for their comments on this work.

Analysis of Deaths from Causes Other Than Clostridial Infection in Relation to Total Dosage of Bacitracin

Bacitracin Units Per Gram	Lot B 471231S			Lot B 480420		
	Animals	Deaths	Mortality	Animals	Deaths	Mortality
30	91	57	63%	42	14	33%
15				42	0	0
10	85	13	15%	16	0	0
5	15	1	7%	10	0	0
4				9	0	0
3				336	8	2%
2				22	1	5%
1				33	3	9%
0.5				25	2	8%
	191	71	37%	535	28	0.5%

POSTOPERATIVE NITROGEN LOSS *

A COMPARISON OF THE EFFECTS OF TRAUMA AND OF CALORIC READJUSTMENT

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OPERATION OR INJURY is generally accompanied by a serious deviation from the individual's customary habits of nutrition and activity. The effects of this change in routine must be considered before any conclusion can be drawn about physiologic alterations resulting from the actual trauma itself. Available information suggests that these factors have not been generally distinguished. Accordingly, when a surgical metabolism unit was established at the Presbyterian Hospital two years ago, one major objective was to provide information bearing on this problem of differentiating more clearly between the effects of operation and changes in routine. This paper presents the nitrogen balance data thus obtained under controlled conditions before and after surgery.

Negative nitrogen balance is considered to occur consistently after trauma to a previously healthy individual. The so-called "toxic destruction of protein," of earlier workers,^{1,3} and the latter-day "catabolic" or "alarm" response attributed to activation of the adrenal cortex, are among the currently accepted hypotheses to explain this nitrogen loss.^{4,9} "Anti-anabolism"¹⁰ is an alternative concept to "catabolism," and postulates that exogenous, *i.e.* food, protein is completely wasted and excreted following injury, thus providing the excess nitrogen found in the urine. A reappraisal of these theories seems advisable in view of the results of the present study.

REVIEW OF PERTINENT LITERATURE

The demonstration that nitrogen is lost to the body in disease was established in the pioneer studies presented at the end of the last century and during the first two decades of this one. The greatest volume of work was done on patients with typhoid fever,^{1,2} but studies were conducted in erysipelas,¹¹ tuberculosis,¹² and other diseases^{13,14} as well. The inability of these early workers to prevent the sharp loss of nitrogen which occurred during the several diseases studied led to the theory that protein is destroyed as a result of toxins released during an infection. These toxins were considered as

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probably injuring cells or specific enzyme systems having to do with protein synthesis and retention. However, Shaffer and Coleman¹ demonstrated that diets with average amounts of protein, but with approximately 75 to 80 calories per Kg of body weight, i.e. about 4000 calories, stopped the loss of nitrogen. They therefore concluded that no such phenomenon as toxic destruction of protein existed. Several years later, however, Coleman and DuBois² measured over brief periods the energy exchange of typhoid fever patients placed in the Russell Sage Calorimeter. From data so obtained they calculated the theoretical caloric requirement of these patients. Despite feeding this amount, nitrogen loss persisted. Accordingly, the workers readopted the "toxic destruction" concept to explain this persistent negative nitrogen balance. It should be noted, however, that their subjects lost weight on what was presumed to be an adequate caloric intake.

Twenty years later, Cuthbertson^{4, 15} observed that fractures were accompanied by a loss of nitrogen to the body both in experimental animals and in man. This loss was greater than that accountable for through local tissue destruction. Cuthbertson was unable to overcome this reaction by increased feeding of protein, and described the phenomenon as a "catabolic response" to injury. In later experiments on rats, however, he¹⁶ and Munroe and Cummings¹⁷ observed that increased provision of protein and calories prevented all systemic loss of nitrogen, that is, loss in excess of that accounted for by local resorption from the injured area.

The war restimulated interest in the phenomena associated with trauma. The fact that increased provision of protein would not overcome the "catabolic response" to fracture was reaffirmed by Howard.⁸ Negative nitrogen balance after surgical operations was noted by Brunschwig¹⁸ and others. Meningitis⁷ was found to cause nitrogen loss. In all these experiments the loss of nitrogen could not be overcome by increases in dietary intake. Albright,^{6, 10} Browne^{9, 10} and others postulated that the adrenal cortex was stimulated by injury, the so-called "alarm reaction" or "adaptation syndrome" of Selye.⁵ As a result of this adrenal activity, either "catabolism" was produced with corresponding breakdown of tissue, or "antianabolism" took place, with inability to utilize incoming nitrogen for protein synthesis and tissue regeneration. These effects were felt to be mediated through the excessive secretion of a hypothetical "S" hormone of the adrenal gland.⁶ Of interest was the fact that depleted subjects readily retained nitrogen upon forced feeding and showed no "alarm" response.

At about this time, contradictory reports began to appear in the literature. Several groups of workers found that the loss of nitrogen after operation or trauma could be prevented by increased dietary intake. Co Tui and workers²⁰ succeeded in this attempt with diets high in protein and calories, the former provided as a casein hydrolysate. Riegel and her associates²¹ were able to define a minimal, although elevated, caloric and protein requirement at which nitrogen equilibrium could be assured after several types of operations.

Werner²² also observed nitrogen equilibrium or marked sparing of expected nitrogen losses when he provided parenteral high protein, as amino acid solution, despite the concurrent administration of low calories. He observed nitrogen equilibrium as well in two patients with fractures and two with burns, excluding exudation and tissue destroyed, and given high caloric high protein regimens by mouth. Hirschfeld²³ overcame the expected urinary negative nitrogen balance in a large series of burn patients, although he questioned the wisdom of the extreme diets which were necessary.

The workers who were able to overcome the nitrogen loss after injury in non-depleted subjects, of necessity have denied that an abnormal mechanism exists consequent to injury. Peters²⁴ has written a critical review of the results obtained by this group, and concludes that proof is not yet at hand that incoming nitrogen can be utilized to prevent the losses consequent to injury in a previously healthy individual.

Werner²⁵ has pursued the subject from a different point of view. He studied the effects of the independent variation of calories and protein in healthy subjects in order to compare the extent of nitrogen loss with those following injury. He was able to demonstrate that such losses are readily sustained for several weeks and occur upon abrupt reduction in calories, or proteins, or both. These losses were comparable in degree to that seen after many operations or after injury. The present study is an extension of this work. In the experiments to be reported, the patient is made to serve as his own control. The same feeding program has been given after surgery as was provided before the procedure. The results have been contrasted to establish the added effects of trauma over those produced by changes in nutrition.

METHODS

All patients in this study were admitted to the Surgical Metabolism Unit of the Presbyterian Hospital, and customary methods for balance studies have been employed, as described elsewhere^{22, 26}. Special nurses and dietitians were provided. A kitchen solely for the use of the unit was set aside. Weighed diets from stocks of food were served, and the nitrogen content of the diet and of the uneaten returns determined by a modified Kjeldahl procedure after homogenization in a Logeman homogenizer. Urine and stools were collected in 24 hour batches but were pooled in three or four day lots for determination of nitrogen content during periods of oral feeding. The determinations were done daily during intravenous nutrition in the postoperative period. Stools were pooled and determined once or twice during a dietary period through the study. Standard methods for the various chemical determinations which were used have been outlined elsewhere^{22, 26}.

All patients were in good health and nutrition, and previously active. They were admitted for interval cholecystectomy or ventral or inguinal hernia repair done by the surgical resident staff, and were subjected to early ambu-

lation Feeding was maintained during the day of operation as well as during standardized pre- and postoperative periods Four groups of patients were studied (Groups I, II, IIIA and IIIB) Protein administration was maintained at a constant level throughout each experiment, but the level of calories was subject to change Reduced caloric intakes were provided in order to insure the same constant intake after operation as before The patients in Group I received a baseline diet by mouth of 30 to 40 calories (Kg body weight) with 12.5 or 14.4 Gm N per day for one week (Period I), then a reduced caloric intake of 18 to 24 calories per Kg with unchanged N intake by mouth for one week (Periods II and III), then operation (Period IV) with provision for the next four days of the same caloric and nitrogen intake but parenterally administered* (Period V), finally a return for three days to the original baseline diet (Period VI) The patients in Group II were maintained as in Group I except that the second weekly period before operation was subdivided Calories were reduced as in Group I except that they were given orally for four days (Period II), then parenterally* for the next three days just prior to operation (Period III) Similar parenteral administration was then continued after the procedure The reason for this preoperative period of parenteral feeding was to document the effect of a shift in route of administration and in quality of the protein source The patients in Group IIIA received a baseline diet for one week as in the first two groups, reduced calories parenterally as described in Group II for four days, baseline calories again for one week, then operation and four days on the same parenteral reduced calories as in the second period, and finally, a return to baseline nutrition The patients in Group IIIB were maintained on the baseline diet with full calories described above for the first week before operation and for ten days thereafter

RESULTS

A total of 26 patients were included in the study There were ten men and 16 women Ages ranged from 18 to 67 There were 11 patients undergoing cholecystectomy, six with ventral hernia repair, eight with inguinal hernia repair, (one bilateral), and one patient with a polyp removed from the colon by colotomy

Group I—Baseline, reduced calories by mouth, operation, and reduced calories parenterally There were five patients in this group, three men and two women The various feeding periods are outlined under the methods section This group was the first studied and hence irregularities appear in the maintenance of constant nutrition in every instance Three of the five patients in the group underwent hernia repair, one cholecystectomy, and one colotomy for a polyp of the colon The average nitrogen balance for the

* Generous supplies were provided of a 10 per cent amino acid solution (VUJ-N) by Dr A Gibson of Merck & Co and of a lyophilized amino acid material, Elamine, by the Interchemical Co, a division of American Cyanamide Corp

various periods of the study is shown in Table I. On baseline intake of calories and nitrogen, the average N balance is $+1.7$ Gm per 24 hours. On reduction of calories with constant N intake by mouth, the average N balance is -0.5 Gm per 24 hours. The balance for the day of operation and the next four days on the same calories and N but given parenterally, as in the period before the procedure, is -3.6 Gm per 24 hours, or a difference of -3.1 Gm N per 24 hours from the preceding period (Table II). The average balance for the last period is -1.1 Gm N per 24 hours.

TABLE I—Showing Average Daily N Balance in the Various Periods Before and After Operation. Patients Grouped According to Feeding Program

Patient Group	No. of Patients	Average N balance (Gm N/24 Hrs)				
		Period I	Period II	Period III	Periods IV & V	Period VI
I	5	$+1.7$	-0.5	-0.5	-3.6	-1.1
II	12	± 0.0	-1.9	-2.3	-2.4	-0.9
III B	6	$+1.2$	$+0.5$	-0.3	$+0.7$	-0.1
III A	3	$+0.2$		-2.4	-4.2	-1.4

Group II—Baseline, reduced calories by mouth, and unchanged low calories parenterally. There are 12 patients in this group, three men and nine women. All the men and four of the women underwent ventral hernia repair while five women were subjected to gall bladder removal. The details of the feeding program are summarized under the methods section. They are the same as Group I except that the period before operation is subdivided

TABLE II—Showing Average Daily N Balance in the Isocaloric Periods Before and After Operation. Patients Grouped According to Feeding Program

Patient Group	Average N balance (Gm N/24 Hrs)		N balance difference Period III—Periods IV & V
	Period III	Periods IV & V	
I*	-0.5	-3.6	-3.1
II	-2.3	-2.4	-0.1
III B	-0.3	$+0.7$	$+1.0$
III A	-2.4	-4.2	-1.8

*Group I inadequately maintained on nutritional schedule (see text)

so that the parenteral feeding given preoperatively (Period III) was duplicated postoperatively (Periods IV and V). The data for the various periods is summarized in Table I. It will be seen that the average daily N balance on parenteral low caloric feeding immediately before operation is -2.3 Gm N while that of the day of operation and of the next four days on the same intravenous feeding is -2.4 Gm. There is a difference of -0.1 Gm N per 24 hours (Table II).

Group IIIA—Baseline, reduced calories parenterally, baseline, operation and reduced calories parenterally. There are three patients in this group, one

man and two women undergoing gall bladder excision. The results are summarized for each period in Table I. It is seen that the average daily N balance resulting from change to parenteral nutrition before operation is -2.4 Gms while the same change in type of feeding after operation produces an average daily N balance of -4.2 Gm. There is a difference between the two periods of -1.8 Gm N per 24 hours (Table II). It should be noted

TABLE III—*Showing Average Daily N Balance in the Various Periods Before and After Operation in Patients Undergoing Cholecystectomy*

Patient Group	Name	Average N Balance (Gm N/24 Hrs)				
		Period I	Period II	Period III	Periods IV & V	Period VI
I	W ₁	+0.9	-0.4	-0.4	-4.4	+1.2
II	At	+1.5	-1.2	-2.3	-2.4	-4.2
II	Be	+1.7	-0.7	-2.4	-3.7	-1.3
II	Ro	+0.2	-2.5	-0.8	-1.9	-0.7
II	Su	± 0.0	-1.4	-4.0	-2.4	+1.6
II	J ₁	+0.7	-1.9	-3.5	-2.8	-0.9
III B	S ₁	+2.9	+2.4	± 0.0	-0.3	-1.7
III B	Ba	+0.3	+0.9	-1.2	-2.4	-1.5
III A	Fe	+0.8		-2.7	-2.7	-0.3
III A	Qu	+1.0		-1.1	-3.4	-0.3
III A*	II ₁	-1.3		-3.3	-6.6	-3.5
†Average		+0.8	-0.9	-2.1	-2.9	-1.0
Range		-1.3 to +2.9	-2.5 to +2.4	-3.5 to ± 0.0	-6.6 to -0.3	-4.2 to +1.6
*Male						
†Average excludes cases in Group I unsatisfactorily treated (see text)						

that one of the three patients had a high temperature following operation and another developed an undiagnosed complication postoperatively.

Group IIIB—Baseline calories throughout. Six patients were maintained on relatively high baseline calories and protein throughout the experiment (Table I). Two were operated on for gall bladder removal, one for ventral hernia repair, and three for inguinal hernia repair. The average N balance

TABLE IV—*Showing Average Daily N Balance in the Various Periods Before and After Operation. Patients Grouped According to Type of Operative Procedure*

Type of Operation	No. of Patients	Average N Balance (Gm N/24 Hrs)				
		Period I	Period II	Period III	Periods IV & V	Period VI
Gall Bladder*	10	+0.8	-0.9	-2.1	-2.9	-1.0
Ventral Hernia	6	-0.2	-1.9	-2.1	-2.3	-0.8
Inguinal Hernia	8	+1.2	-0.4	-0.7	-1.0	-0.4
Partial Colectomy	1	-1.0	+1.4	+1.4	-0.6	-0.8

*One case in Group I excluded because of unsatisfactory maintenance of nutrition.

for each period is summarized in Table I. No significant change in nitrogen balance is seen following operation (Table II).

EFFECT OF OPERATIVE PROCEDURE

The cases in the above groups have been reclassified according to the type of operative procedure, without regard to nutritional schedule (Tables

III, IV, and V) A comparison of the isocaloric periods before and after operation reveals no significant difference in nitrogen balance between the pre- and postoperative periods of each of the surgical procedures studied. No significantly greater degree of negative balance is noted for one procedure over another (Table V). A daily balance difference average of -1.0 Gm N is seen for the gall bladder subjects between the pre- and postoperative periods, of -0.2 Gm N for the ventral hernia, and -0.3 Gm N for the inguinal hernia patients. The results are even slightly better if the irregularly fed

TABLE V—Showing Average Daily N Balance in the Isocaloric Periods Before and After Operation. Patients Grouped According to the Type of Operative Procedure

Type of Operation	Average N Balance (Gm N/24 Hrs)		N Balance Difference Period III—Periods IV & V
	Period III	Periods IV & V	
Gall Bladder*	-2.1	-2.9	-0.8
Ventral Hernia	-2.1	-2.3	-0.2
Inguinal Hernia	-0.7	-1.0	-0.3

*One case in Group I excluded because of unsatisfactory maintenance of nutrition

cases in Group I are excluded. Two of the ten gall bladder patients fed without interruption showed negative nitrogen balance increases of more than 1.5 Gm N per day after operation.

EFFECT OF MAINTENANCE OF CONSTANT NUTRITION

The cases in the original groups have been regrouped according to the success with which constant isocaloric nutrition was maintained through the

TABLE VI—Showing Average Daily N Balance in the Isocaloric Periods Before and After Operation. Patients Grouped According to Success in Maintenance of Nutritional Schedule

Maintenance of Therapy	No. of Patients	Average N Balance (Gm N/24 Hrs)		N Balance Difference Period III—Periods IV & V
		Period III	Periods IV & V	
Poor	5	-0.5	-3.6	-3.1
Fair	6	-2.1	-2.8	-0.7
Complete	15	-1.5	-1.3	+0.2
Fair and Complete	21	-1.7	-1.7	± 0.0

experiment. The results for the periods immediately before operation and following are summarized in Table VI. A significant increase in negative nitrogen balance following surgery is noted only in those patients in whom sharp irregularities in nutrition occurred—the “poor” classification. These latter show a difference in average daily nitrogen balance between the pre- and postoperative periods of -3.1 Gm N as opposed to -0.7 Gm N for the “fair” category and 0.2 Gm N for the “complete success” group. The average daily difference in N balance after operation from before is ± 0.0 Gm N for the combined “fair and complete success” groups.

POSTOPERATIVE NITROGEN LOSS

EFFECT OF CHANGE FROM BASELINE TO LOW CALORIC FEEDING PREOPERATIVELY

Table VII shows the effect of a sudden change from relatively high levels of caloric intake, often insufficient to maintain body weight, to lower ones, *i.e.* from 30 to 40 calories per Kg body weight to 18 calories per Kg body weight. Protein intake was kept throughout. The same sharp negative nitrogen balance following caloric reduction occurs as has been reported elsewhere²⁵

TABLE VII — *Showing Average Daily N Balance in the Periods of High and Low Caloric Feeding Prior to Operation*

Patient Group	Average N Balance (Gm N/24 Hrs)		N Balance Difference Period I—Period II
	Period I	Period II	
I	+1.7	-0.5	-2.2
II	0.0	-1.9	-1.9
III A	+0.9	-1.9	-2.8

Table VIII demonstrates the average daily nitrogen balance which results upon change to intravenous from oral administration of a low caloric constant protein intake. No significant difference is found in the average for this group as a whole. However, five of the 12 patients show an increase in negative nitrogen balance of more than 1 Gm N per 24 hours (-2.0, -1.9, -1.8, -1.3 and -1.1 Gm N per 24 hours), as a result of shifting to intravenous administration.

TABLE VIII — *Showing Average Daily N Balance in the Isocaloric Periods Before and During Intravenous Feeding Prior to Operation*

Patient Group	No. of Patients	Average N Balance (Gm N/24 Hrs)		N Balance Difference Period II—Period III
		Period II	Period III	
II*	10	-1.9	-2.3	-0.4
III B*	2	+1.6	-0.6	-2.2
	Average	-1.3	-2.0	-0.7

*Does not include patients fed orally through Period III

DISCUSSION AND CONCLUSION

Published studies concerning the extent and causation of body nitrogen losses which follow injury have not differentiated between the loss due to the actual trauma and that due to the inevitable changes in type of nutrition which accompany injury²⁸. Such a distinction appears necessary in order to evaluate the effect of trauma, and may help explain why divergent opinions exist about the consequences of injury.

The present report concerns the results of a study in healthy patients undergoing cholecystectomy and ventral and inguinal hernia repair. It has been generally accepted that nitrogen loss follows these surgical procedures,

although there has been disagreement as to whether this loss can be overcome by dietary means in the case of the gall bladder operation. However, the data obtained in the current study reveal that no loss of nitrogen is found following a surgical procedure beyond that observed on the same caloric intake before the operation. This lack of response to the injury of operation is not explainable by previous depletion, since the patients were in good health, had lost no weight, and had had no recent infection. The failure of excesses of nitrogen to appear in the urine is difficult to harmonize with the concepts that abnormal mechanisms are invoked by trauma, namely, increased tissue destruction—"catabolism," or arrested utilization of exogenous, i.e. administered, nitrogen "anti-anabolism."

Cholecystectomy, or hernia repair, may not be severe enough forms of injury to invoke these mechanisms, or may do so only occasionally. However, nitrogen loss has hitherto been regularly described after these operations^{18, 29} when no increases in nutrition were provided. If this nitrogen loss is the result of inadequate nutrition, as appears to be the case, it becomes necessary to reexamine the reports concerning negative nitrogen balance following other operations and injuries in order to define the extent to which caloric deficits may have contributed to the total.

Such caloric deficits may be exaggerated by the additional caloric requirements resulting from fever. Furthermore, the estimation, and hence provision, of such needs is made difficult by inaccuracies in the measurement of heat production during constant fever and during periods of temperature change. Much information is available from the studies of patients with typhoid fever.²

The losses of nitrogen which occur during this latter disease were avoided by Shaffer and Coleman¹ by feeding high caloric regimens during the course of the disease. These workers denied the existence of abnormal mechanisms in the handling of nitrogen. Coleman and DuBois² revived the hypothesis of "toxic destruction" when they found persistence of negative nitrogen balance after feeding a theoretically adequate amount of calories as determined from calorimeter measurements. The weight loss of their patients indicates that their estimate of caloric need may have been faulty. Calculations based upon the concept that the law of conservation of energy pertains to these subjects indicates that an additional 1000 calories, or about 4000 calories total, might have maintained weight, and this is about the amount which prevented nitrogen loss in the work of Shaffer and Coleman. Apparent discrepancies from the law of conservation of energy exist²⁷ and it is possible that typhoid fever patients fall in a separate and intermediate category in terms of abnormal or "anti-anabolic" mechanisms produced by this disease as compared with operation and other types of infection.

A true "anti-anabolism" appears to follow recovery from scarlet fever and meningitis, according to Peters and his group.⁷ Nitrogen is burned and excreted to the same extent as fed, by these subjects, despite elevated levels

of protein and caloric administration. This finding suggests the possibility that the presence or absence of infection may account for some of the discrepant results obtained by different workers attempting equilibrium following more severe injuries and operations than those reported in the present study. Infection not infrequently accompanies more radical surgery or trauma and may be masked for some time, whereas it was not a complication of the procedures reported here, except possibly in one instance. Should infection be the variable which is responsible for the appearance of abnormal mechanisms in the handling of nitrogen in some cases and not in others, it is of importance to recognize this in reporting on the effect of trauma. It is also necessary to take into account the effects of added caloric requirements resulting from such a complication. Otherwise mis-impressions may be gained about the consequences of injury by itself. Thus, the one male patient undergoing cholecystectomy had a moderate fever in the immediate postoperative period and a hidden covered infection which became manifest only later in the postoperative period. He does not therefore represent the nitrogen loss from uncomplicated operation.

Added support for the view opposing the existence of abnormal mechanisms consequent to injury uncomplicated by infection, is found in recent animal experiments^{30, 31}. In the presence of a constant supply of adrenal cortical hormone given to adrenalectomized animals, loss of nitrogen occurs after injury exactly as in animals with intact adrenals. No increase in adrenal secretion is possible in the former animals, yet an "alarm" response is found. Thus activation of the adrenal cortex is ruled out as a mechanism to explain the negative nitrogen balance following injury, except as a functioning adrenal enables the body as a whole to react adequately.

In conclusion then, evidence is brought forward that certain operations are not accompanied by nitrogen loss beyond that produced by the same nutritional regimen provided before surgery. Lack of excessive nitrogen excretion is difficult to harmonize with the concept that abnormal mechanisms for the handling of protein have been invoked by the operations concerned. Interruption of nutrition, even if transient, produces nitrogen losses not compensated for by corresponding increases a day or so later. This is probably explained by the fact that nitrogen cannot be stored unless a definite minimum requirement of calories is also provided³². This minimum is greater than that generally furnished after operation, and is not attained by the slight increases in caloric intake mentioned immediately above. These losses should not be attributed to the effect of the trauma of operation. The role of infection has not been studied, and may well invoke responses not found following the operations reported here.

SUMMARY

1. Twenty-six healthy and non-depleted patients have been studied with the purpose of distinguishing the effect of the usual changes in dietary intake, postoperatively, from the effects of the trauma of operation *per se*.

2 Eleven patients in otherwise good health underwent cholecystectomy, six ventral hernia repair, eight inguinal hernia repair, and one colotomy.

3 The effect of shift from relatively adequate calories to the lower caloric intake usually given after operation has been studied preoperatively. This latter diet was then continued through the day of operation and beyond. Protein in the diet was kept constant. No significant increase in nitrogen output resulted from the operative procedure.

4 The implications of these findings have been discussed. The concept is proposed that simple caloric lack explains the postoperative nitrogen loss found following operation uncomplicated by infection.

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DISCUSSION—DR CHAMP LYONS Our group at Tulane has been similarly interested in the problem of negative nitrogen balance following operative trauma. Unquestionably, restricted oral intake is responsible in considerable degree for the observed negativity of the balance. It occurred to us that it would be helpful to know whether or not protein made available by mouth or vein would be retained or rejected during the postoperative period of negative balance. Experiments were designed to study this simple problem without attempting to determine the ultimate utilization of retained nitrogenous substances within the body. Two types of experiments have been done.

Glycine synthesized to contain N_{15} has been fed as dietary supplement to healthy adults and the percentage of N_{15} excreted in the urine has been followed. The administration of adrenocorticotrophic hormone (ACTH) to these subjects at the time of feeding tagged glycine has produced an increased total excretion of N_{15} . However, all of these subjects had previously had other studies with N_{15} and we cannot state that the ACTH effect was directed solely at the newly ingested N_{15} . It may ultimately be shown that some of the excreted N_{15} was mobilized from previously fed and retained nitrogen.

The expense of N_{15} has discouraged its extensive use. In order to continue these observations on a wider scale, the urinary clearance of intravenously injected amino acids, as suggested by Eckhardt and Davidson (*J Clin Investigation*, 27 727, 1948), were adapted to our purpose. Patients were placed on the metabolic division with nitrogen balance studies. Pre-operative and postoperative amino nitrogen clearances were performed. A series of normal subjects and surgical patients have been studied.

A typical experiment may be summarized as follows

Slide 1 Two control periods of one hour each preceded the injection of Merck's VUJN mixture. The percentage of amino-N excreted in the urine during these control periods was negligible. The injection of amino acids required approximately 1 hour. Six per cent (6%) of the total amino N injected was excreted with the patient in N balance. This is a low figure, inasmuch as normal subjects may excrete up to 10 per cent of the total injected.

Slide 2 One day following radical mastectomy the patient was in negative nitrogen balance with reduced oral intake. A lag in the rate of urinary excretion is noted, but the quantity of amino-N excreted amounts to only 7.5 per cent of the total injected.

Slide 3 On the third postoperative day the nitrogen balance was still slightly negative. The rate of excretion was somewhat improved, but the total excreted was still 7.5 per cent.

Slide 4 On the eighth postoperative day the patient was ambulatory and eating well. The nitrogen balance was positive. The urinary excretion rate had returned to the pre-operative pattern, and the total amino-N excreted was 8 per cent of that injected.

Conclusions Although it seems likely that ACTH increases the rate of excretion of newly available protein substrates, we have been unable to demonstrate accelerated excretion of injected amino-N in postoperative patients in negative nitrogen balance.

PARTITION OF URINARY NITROGEN

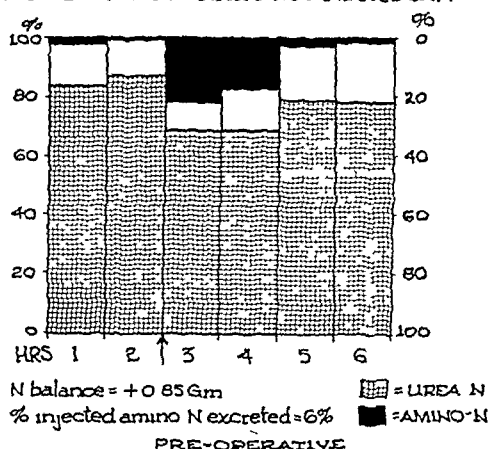


CHART I

PARTITION OF URINARY NITROGEN

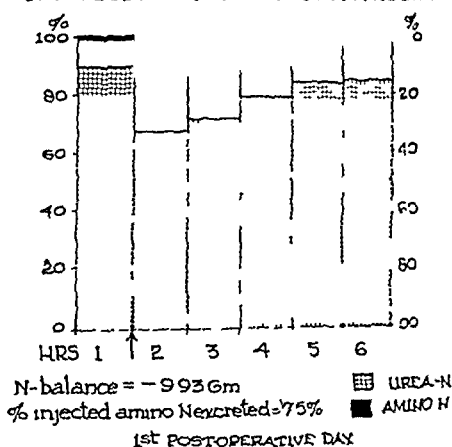


CHART II

PARTITION OF URINARY NITROGEN

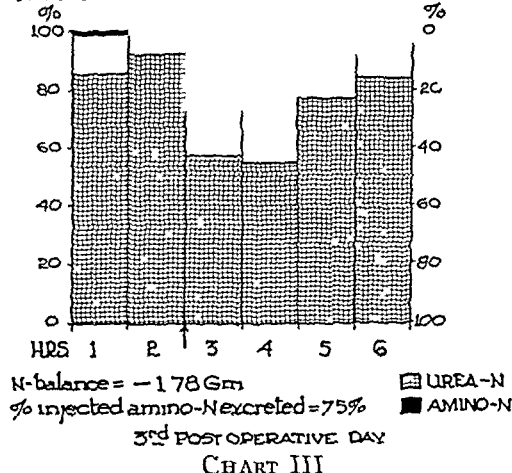


CHART III

PARTITION OF URINARY NITROGEN

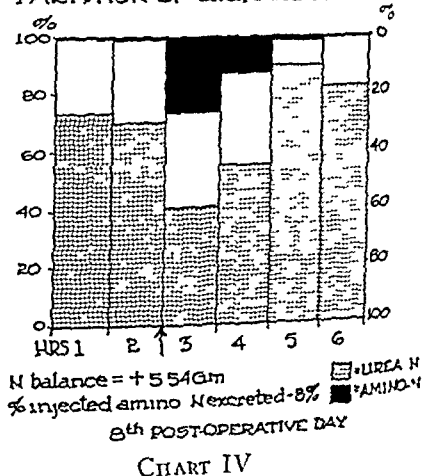


CHART IV

POSTOPERATIVE NITROGEN LOSS

DR OLIVER COPE, Boston, Mass Dr Werner and his colleagues have rightly tried to differentiate the negative nitrogen balance due to starvation from that due to a possible theoretic, so-called alarm reaction of endocrine origin

It is an enormous help to us to have internists like Dr Werner, schooled in metabolic observation, to guide us through these problems Dr Werner has demonstrated that in operations of the type mentioned, and under conditions under which the operations are carried out, starvation accounts for what negative nitrogen balance there is

On the other hand, I would like to point out that these patients were for a long time conditioned to the hospital prior to the operation I was brought up by my older surgical teachers to realize that no patient was a better operative risk than an old patient with a gallbladder who had been in bed for a month prior to operation

In contrast to Dr Werner's results are the observations of Dr John Howard at Johns Hopkins, who showed that the nitrogen balance, or metabolic reaction of the patient to operation and trauma, varied according to the size of the trauma, and also to the health of the patient He showed that a patient with a traumatic compound fracture of the femur, who was well, healthy and vigorous before the accident, had an enormous so-called catabolic reaction, whereas in a patient who had been sick and was in a chronic debilitated state prior to the fracture, no such reaction occurred, and the patient had a nitrogen balance like that which Dr Werner has described

This is a knotty problem, hard to pick to pieces, and I am certain that it is by such careful studies as Dr Werner has presented to us that eventually we will know the origin of the reaction to operation and how to meet it

DR DAVID V HABIB Dr Lockwood asked me to say a few words in regard to the paper I should like to say first that the patients were selected only because they were healthy, without previous weight loss, and because they were willing to spend an extra two-week period pre-operatively on the surgical metabolism service to serve as their own control, as Dr Werner has already mentioned

All patients were operated on by the resident staff, so that they were not selected in the sense of having a fine or rapid operation by skilled attending surgeons

The caloric intake decided upon was the amount that could be met parenterally both pre- and postoperatively We have heard of the high concentrations of glucose given elsewhere without thromboses but these patients received only 7½ per cent glucose with at times alarming thromboses of arm veins It would appear that the length of time the needle is in the vein is important, and the resulting thromboses are a limiting factor in this type of experiment

Another complicating feature arose which was not appreciated beforehand in that in some patients there was a much greater loss of glucose in the urine postoperatively Since quantitative urine glucose determinations were done both pre- and postoperatively, and the amounts administered intravenously were the same, it was found that up to 112 Gm of glucose were lost postoperatively Pre- and postoperative glucose tolerance tests have been found to be the same, so that at present we have no explanation, and the problem is under study

We are all familiar with the fact that minor complications postoperatively do influence nitrogen balance, so that in such a study as has been presented it is important to judge the effect of operation alone and not operation plus perhaps an obscure minor complication

Not only is it impossible with present-day facilities in many instances to give sufficient calories to prevent a negative nitrogen balance and weight loss following trauma or operation, but it appears impossible to quantitate the requirement For example, working with Dr John Nickerson of our Department of Physiology, we have studied the cardiac outputs of some of these patients with the ballistocardiograph which he designed There appears to be a marked increase in cardiac output not suspected from clinical observation alone, and this work of the heart in itself would require a considerable number of calories As

well, the B M R done both before and after operation showed that there is more than the expected ten per cent rise per degree of fever in the immediate postoperative period

This study was concerned chiefly with investigating the mechanisms involved in nitrogen loss following trauma, and if the conclusions are true, that the excess nitrogen loss is due to insufficient calories, it should be possible, in the long-term case, by providing such calories, to maintain positive nitrogen balance without weight loss. This is the aim of current studies

DR SIDNEY C WERNER, New York, N Y My lengthy preliminary remarks have resulted in my being unable to make some of the statements which I might have made to anticipate what Dr Cope has justly brought up

The question of whether more severe trauma can be compared with the lesser degree of trauma which follows gallbladder removal, ventral hernia repair, and so on, is naturally a cogent one. One would have to study each type of procedure in order to gain information which one would consider as proof. However, I do not think it unreasonable to suspect that if the body reacts to trauma in a given way for one degree of injury, that the reaction will be the same with more severe traumata

One big factor in all such work is the control over the added caloric requirements of resultant fever. Hirschfeld, with large amounts of calories and protein, has been able to restore nitrogen equilibrium in burn patients, and in our own hands we were able to do the same. Moreover, in a patient with a burn or a compound fracture, there is the added factor of infection, which must be accounted for. Also, for the first few days, adequate feeding is not generally given, protein is drawn upon as a fuel, and so the body becomes adapted to a high rate of nitrogen turnover. This creates a lag in adjustment to diets with less nitrogen and nitrogen losses may persist for a week or so just on this account. In experiments with normal people given a high level of nitrogen intake, this outpouring of nitrogen will persist when the intake level is reduced to normal for some time after the change in diet. All of these influences have to be evaluated before the presence or absence of abnormal mechanisms can be established

Dr Lyons' discussion was very much to the point, and reminds me of several animal experiments which I mentioned earlier, by Noble and by Ingle, which indicate, also, no abnormal mechanisms follow injury. They found that following adrenalectomy in the experimental animal, the rat, if one gives adrenocortical extract in a constant amount before and after operation, one gets a typical alarm response and an outpouring of nitrogen, despite the fact that there is no possibility of the adrenal cortex suddenly secreting an excess of adrenocortical steroids. It would appear, therefore, that the function of the adrenal is to permit the body to react adequately to its needs following trauma, rather than that the adrenal is responsible for the nitrogen loss which follows trauma

It should be stressed that this discussion of injury does not necessarily apply to the factor of infection which may be something else again

MINIMUM POSTOPERATIVE MAINTENANCE REQUIREMENTS FOR PARENTERAL WATER, SODIUM, POTASSIUM, CHLORIDE AND GLUCOSE*

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UNDER NORMAL CONDITIONS of oral intake it is sometimes but not always easy to assure an adequate nutritional intake for the surgical patient. When the patient is unable to take anything by mouth and all intake must be parenteral, the responsibility of the surgeon increases, for while a definite measurable intake is more readily achieved, it is more difficult to know just how much of each element should be injected. Indeed, it is important to know just how little may be injected, i.e., the minimum needs to maintain normal function. Such knowledge is of practical value because it will avoid the inconvenience and expense of unnecessary, and the danger of excessive, injections. In order to study the probable minimum requirements, a series of observations were made on surgical patients given daily 2000 cc of fluid containing glucose with and without added sodium chloride for four post-operative days. The findings suggest that a smaller intake of both water and salt than is usually given seems to be adequate. Moreover, specific data on potassium losses and glucose utilization were also obtained.

PREVIOUS WORK

The basis upon which surgeons estimate the water, electrolyte and glucose needs for the parenteral maintenance of the postoperative patient is, to a considerable extent, theoretical and traditional. In the early days of parenteral therapy large volumes were given, as much as four and five liters per day, not for the correction of deficits, but for maintenance of normal water balance. This was perhaps part of the then general belief in the value of a large fluid intake as illustrated by the still frequent order "force fluids." More significant than the large volumes injected was the fact that these fluids contained 9 Gm of salt per liter because this was the only way in which isotonicity was achieved. Even when glucose was added later, the influence of tradition on the need for saline was not changed. Thus the amount of salt injected was often as great as 27 or even 36 Gm per day, which is three to four times the intake of a normal individual. As might be expected, difficulties due to retention of fluid were produced though for a long time the casual connection was unrecognized. These difficulties were serious,

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and sometimes led directly to a fatal outcome. They arose because the human kidney could not excrete the large amount of salt, and therefore retained water with it to maintain the osmotic pressure of the body fluids. The clinical effects of this tremendous increase in body fluids were manifold—pulmonary edema, wound disruptions, peritonitis from failure of apposed peritoneal surfaces to heal, and circulatory impairment. So common did this danger become that Coller and associates² sounded an emphatic warning in 1944 in a report entitled *Postoperative Salt Intolerance*.

At the present time, most surgeons give the average adult postoperative patient unable to take anything by mouth 3000 cc of water parenterally for maintenance alone, more to correct abnormal losses. Of this, one liter generally contains isotonic salt, so that the sodium chloride intake is nine Gm a day, the amount an average normal individual is supposed to ingest in an average normal diet. Actually this may be much smaller, as indicated by analyses we have made on a number of patients on the usual hospital diets. As to glucose, the practice varies, some using 5 per cent glucose with or without amino acids, others a combination of 5 and 10 per cent glucose with or without amino acids. The intake of glucose and amino acids with three liters thus varies from 100 to a maximum of 300 Gm of each.

Specific data on the minimum water, salt and glucose needs are rather limited. Cooper, Iob and Coller³ have carried out carefully controlled studies of the urinary response for a period of only 30 hours after infusions of 5 per cent glucose in normal men and in patients following operations of varying magnitude. They observed a definite postoperative oliguria which was associated with a minimal output of sodium and chloride. Patients undergoing less severe operations, such as herniorrhaphy, as well as abdominoperineal resection, both experienced periods of low water output which later changed to diuresis. Sodium and chloride were excreted more rapidly during the periods of low water output, but were conserved during the diuresis stage. The average sodium loss was less (47.3 meq) after abdominoperineal resection than after herniorrhaphy (107 meq). Berry, Iob and Campbell,¹ in the same patients measured the potassium output in the first 30 hour postoperative period and found losses from 30 to 119 meq. The younger patients excreted more potassium than older ones undergoing the same operation, and those who had the more severe operative procedure, e.g., abdominoperineal resection excreted on an average 73 per cent more free potassium than the controls who did not undergo any operation, or those subjected to herniorrhaphy. Howard¹³ studied chronically ill surgical patients given an intravenous intake for six preoperative and six postoperative days. He found that on a constant intake of sodium and chloride (about 12 Gm daily), despite considerable individual variations, most patients showed retention of salt after operation. He also found that on an intake of 50 meq a day, more potassium was lost immediately after than before operation. The greatest loss occurred

during the second postoperative day This agrees with the findings of Reifenstein¹⁶ who studied a patient after spinal fusion Reifenstein also found that urinary excretion of sugar or reducing substances was increased after operation The type of anesthesia and duration of operation are not mentioned

PROCEDURE AND METHODS

In order to study this problem of minimum water, salt and glucose needs, balances were measured in a series of patients We adopted first of all a volume intake of 2 liters, basing this on theoretical considerations In various groups glucose was given in two concentrations, 5 and 10 per cent, in the latter concentration one series contained no salt intake, in another the intake consisted of 9 Gm a day

In all, 40 surgical patients were studied They were unselected except for the criteria that they must have no clinical evidence of cardiovascular or kidney disease The operations performed varied, although most of them consisted of uncomplicated cholecystectomy Their preparation for operation did not necessitate special regimens such as blood, chemotherapy, etc The preoperative medication was morphine and atrophine All anesthesia was induced with sodium pentothal followed by gas-oxygen-ether Nearly all cases were studied for an arbitrary experimental period of four consecutive days or 96 postoperative hours A few patients were also studied before operation During this time all intake was by intravenous injection Any patient with a source for abnormal postoperative fluid or electrolyte loss (i e, vomiting, biliary or gastro-intestinal drainage exceeding 100 to 200 ml) was eliminated Urine was collected during 24 hour periods and measured, an aliquot was obtained and preserved with toluol and refrigeration The electrolyte content of small amounts of emesis occurring during the first postoperative day was included in the first 24 hour specimen Heparinized samples of blood were withdrawn before operation and at the end of the study Specific gravity and pH of the urine were determined by hydrometer and by glass electrode respectively The urines were analyzed for sodium and potassium by means of the Weichselbaum-Varney flame photometer,²⁰ for chlorides by the method of Harvey,¹¹ for total nitrogen by the macro-Kjeldahl method of Hiller, Plazin and Van Slyke,¹² for creatinine by the method of Folin⁷ adapted for the spectrophotometer, for acetone by the Legal nitroprusside test, and for sugar by the method of Somogyi,¹⁷ for inorganic phosphates by the method of Fiske and Subbarow⁶ The plasma was analyzed for sodium and potassium by means of the Weichselbaum-Varney flame photometer,²⁰ for chlorides by the method of Van Slyke and Hiller,¹⁹ for N P N by the method of Folin⁷ adapted for the spectrophotometer, and for plasma proteins by the method of Weichselbaum²¹ Hematocrit measurements were done on heparinized blood in a Wintrobe tube

Blood transfusions were given several patients following operations other than cholecystectomy. The amount of blood was estimated to replace that lost during operation. In calculating balances no allowance was made for the electrolyte content of this blood except for the sodium citrate it contained. None of the patients undergoing cholecystectomy required blood replacement and it is this group of patients which were studied in greatest detail. These were divided into three groups.

One group of patients undergoing uncomplicated cholecystectomy received daily infusions of 2 liters of 10 per cent glucose in water, a second group

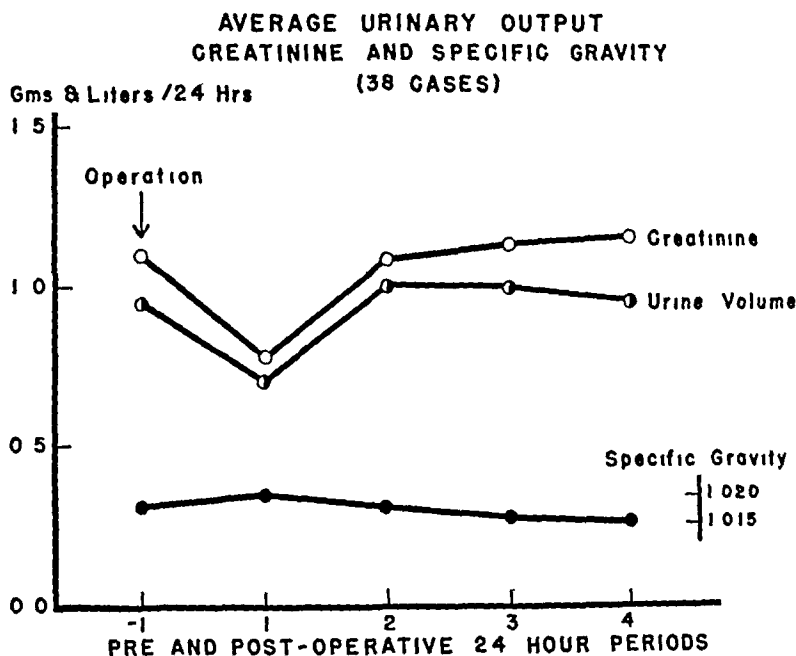


FIG 1—The graph represents the averages in 38 patients receiving an intake limited to 2 liters of intravenous glucose per day. Statistical analysis reveals that the changes from day to day were significant. Note the constancy of the specific gravity and the parallel fall in the creatinine content and urine volume in the first postoperative 24 hour period. Note also that after the first day the urinary output averaged one liter per day, which would be considered adequate.

received 2 liters of 10 per cent glucose in water to each of which $4\frac{1}{2}$ Gm of sodium chloride had been added, and a third group received 2 liters of 5 per cent glucose in water. Each patient's first infusion was started between 8 and 9 A.M., and his second between 4 and 5 P.M. The duration of each infusion was approximately three hours. There was no oral intake during the period of study. All patients were observed during the fall, winter and spring months.

FINDINGS

The findings are described under three headings: water, electrolyte and glucose.

Water—The findings dealing with water balance are limited to measurements of urinary volume, creatinine, and specific gravity. Figure 1 shows the average daily pre- and postoperative values of 38 patients whose daily infusions consisted of 2 liters of 10 per cent glucose in water or 2 liters of 10 per cent glucose in water containing a total of 9 Gm of NaCl. The addition of salt did not influence these findings. One notes that the daily urinary output approaches a liter per day except during the first 24 hour postoperative period. During this day the urinary output averages 750 ml in comparison to 930 ml for the day prior to operation, and 1000 ml for the second and third postoperative days. These figures were subjected to careful statistical analysis and found to be significant in their day to day difference.

The oliguria noted during the first 24 hours after operation is accompanied by a fall in creatinine output, but without any change in specific gravity. Not every patient experienced this oliguria and the degree varied. The ages, which ranged from 19 to 75, did not seem to be a factor. The severity of the operation may be a factor but the number of various procedures studied was insufficient to draw definite inferences. Blood replacement at the time of operation in 12 cases did not seem to prevent oliguria during the first 24 postoperative hours. The operative records of these patients were examined and none had significant hypotension during their operations. In spite of the relatively normal urinary output, many of these patients experienced variable degrees of thirst which might indicate that the water intake was too low despite the adequate urinary output. However, there was no certain indication that this thirst was any different than it is in patients who received 3 liters of water. Controlled observations of this subjective symptom are difficult but perhaps deserve more study.

Electrolyte—First of all are the observations on patients receiving no salt at all. These include 21 patients whose data are summarized in Table I. The operations were of various kinds, but the intake in all patients was limited to two liters of 10 per cent glucose intravenously a day. Scrutiny of these data reveals the fact that on no electrolyte intake and despite much individual variation, there is a conservation of salt as shown by a gradual decrease in the amount of sodium and chloride excreted on each consecutive day during the four day postoperative study period. Patients who received blood replacement on the day of operation tended to lose on an average slightly more sodium and chloride than those not needing blood replacement. In general, those receiving blood were the ones subjected to a more severe operation.

Age proved to be a factor in the individual variations in electrolyte conservation as shown by the data in the six cholecystectomized patients listed in Table I, three were young, aged 19, 27 and 28, and they excreted daily, over the 96 hour study period, an average of 7 meq of Na and 17 meq of chloride, in contrast to the older patients, aged 56, 59, and 64, who excreted twice as much, i.e., 20 and 34 meq respectively. Thus, with no electrolyte

TABLE I—Postoperative Output in Urine Per 24 Hours
Daily Intake 2000 cc 10 Per Cent Glucose in Water

Case	Age Sex	Op	Postoperative 24 Hour Periods												Cumulative Loss											
			1				2				3					4										
			Na	K	Cl	P	Na	K	Cl	P	Na	K	Cl	P		Na	K	Cl	P							
1	19F	GB	28	45	37	24	3	19	14	30	13	6	13	13	13	7	4	2	7	13	11	6	62	79	93	18
2	56F	GB						36	57	44	37	7	12	35	24	18	6	5	12	21	4	8	53	104	81	20
3	54F	GB	53	23	59	9	2	40	24	45	20	4	21	14	33	2	4	13	5	20	0	2	126	66	156	13
4	28F	GB	13	27	13	26	6	3	11	14	12	5	2	8	7	12	5	2	6	3	8	4	20	53	37	20
5	59F	GB	51	25	79	16	2	18	33	23	34	3	14	20	15	5	5	3	13	4	10	3	86	93	123	12
6	27F	GB	19	15	31	14	2	11	30	27	33	5	3	4	14	16	4	1	17	5	24	7	33	66	77	18
7	75F	GR*	32	18	29	15	4	30	23	24	17	8	52	44	43	35	11						114	84	93	19
8	53F	GR*	40	21	40	26	5	81	28	17	28	8	33	50	65	38	22	31	27	47	8	14	184	128	162	49
9	72M	GR*	23	39	23	20	4	52	54	48	26	6	61	41	65	22	7	23	31	127	20	6	164	165	257	23
10	74M	JC	30	23	32	35	6	17	17	25	58	5	23	15	33	9	5						70	54	89	16
11	58F	JE	5	2	12	1	3	6	2	12	1	2	7	2	10	5	2	2	8	33	12	6	20	14	63	13
12	59F	HY*	96	69	70	30	7	83	38	20	28	8	24	21	14	18	6	107	17	14	10	4	157	145	119	25
13	42F	HY*	19	36	42	3	4	15	37	34	5	7	7	19	19	10	6	5	14	17	15	8	44	106	111	25
14	41F	HY*	62	72	68	67	5	53	31	36	32	6	41	28	58	23	6	13	17	33	8	4	167	147	195	21
15	39F	HY	63	42	73	48	4	38	31	57	27	3	45	54	48	13	2						146	127	179	8
16	39F	HY	42	38	27	8	3	8	38	23	6	8	8	10	22	33	11	8	20	15	43	10	66	105	87	32
17	37F	HY*	43	83	56	77	7	14	50	45	56	9	21	55	30	43	21	3	13	22	18	6	81	201	153	43
18	13F	RM*	60	75	62	67	7	37	66	83	49	8	16	30	41	18	8	22	38	59	36	11	144	209	245	34
19	10M	IH	18	13	26	12	3	30	42	53	37	10	9	51	47	38	10	7	24	29	38	10	64	129	157	32
20	31F	TH	101	112	91	99	11	10	17	23	49	4	11	16	14	35	4	11	14	18	24	4	134	157	146	23
21	32M	EL*	21	7	13	31	4	20	29	11	65	10	6	12	19	10	9	16	39	13	24	7	62	88	65	30

Key Sumc is in Table III

intake, the younger patients seem able to conserve more Na and Cl than the older patients, when each is subjected to the same operation under similar conditions

The pattern of electrolyte loss on no salt intake is shown graphically in Figure 2, which is based on the six cholecystectomized patients already mentioned. Although there were considerable individual variations, the average figures picture accurately the trend in all, i.e., the gradual fall in the amount of Na and Cl excreted, thus showing an efficient conserving

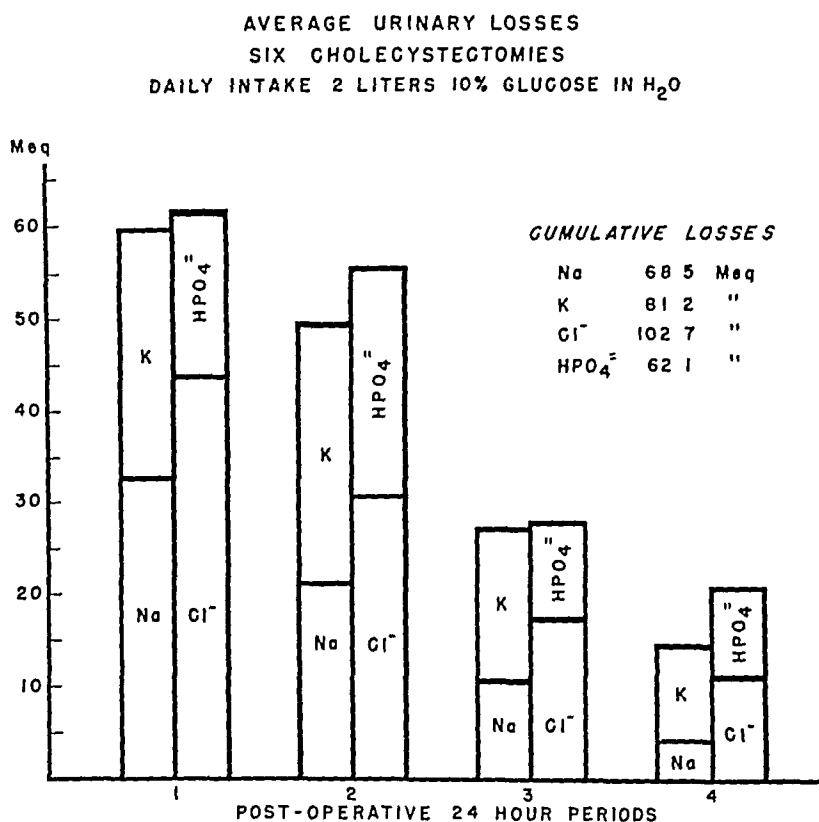


FIG 2—There was no salt intake in these patients. Note the decreasing output of sodium and chloride ion due to a conserving mechanism. Note, however, that the total average sodium loss during the 96 postoperative hours as sodium chloride was about 4 Gm. Note that the loss of potassium is more uniform and amounts, by the end of the 96 hour period, in terms of potassium chloride to 6 Gm.

mechanism for these ions in the absence of any intake. On the other hand, potassium and phosphate tended to be excreted at a uniform rate during the first two 24 hour periods, and in some cases had a greater output during the second 24 hour period than during the first. The 96 hour cumulative loss was fairly small (Na 68 meq, K 81 meq, Cl 103 meq, HPO₄ 62.1 meq, N 16.9 Gm) and represents about 4 Gm calculated as NaCl and 6 Gm calculated as KCl. It is not surprising, therefore, that this loss was accompanied by no significant changes in the blood levels of these electrolytes nor by any

alteration in the CO_2 combining power, serum protein or hematocrit (Table IV)

In order to compare the salt loss before with that after operation, one patient (Fig 3) was given glucose in water during two preoperative periods. The same decrease in output of Na and Cl was again seen. The operation *per se* did not seem to affect this pattern of salt conservation in that the progressive fall in excretion of Na and Cl continued. On the other hand, potassium and phosphate behaved differently, i.e., more was excreted post-operatively, especially in the second postoperative 24 hour period.

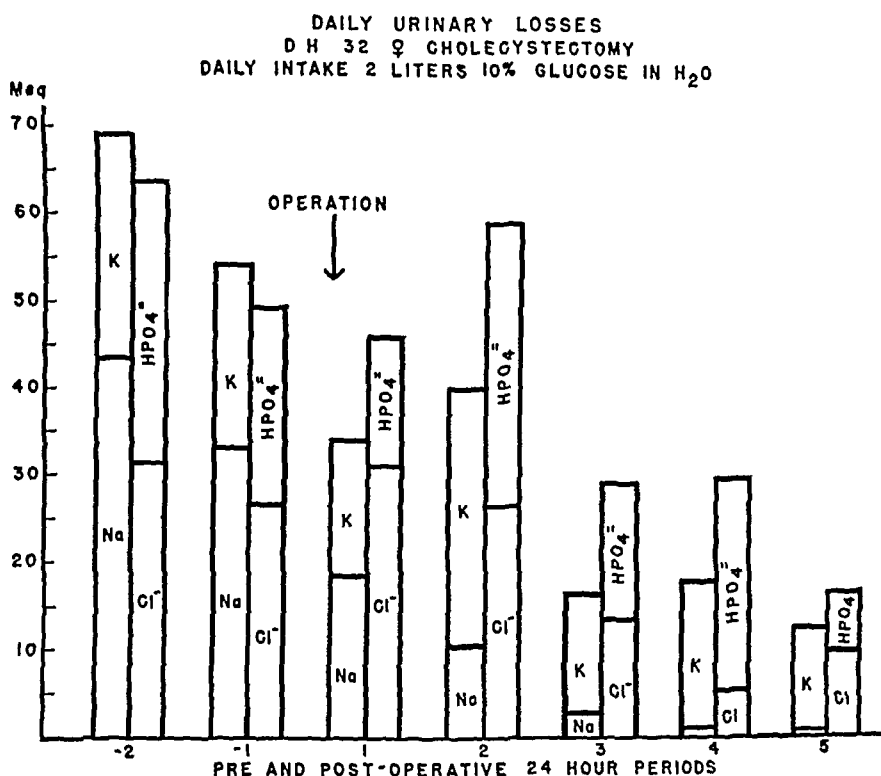


FIG 3—Pre- and postoperative urinary losses in electrolyte. This patient was given no salt before or after operation. Note that the pattern of conservation of sodium and chloride ion is not influenced by the operation. On the other hand, note the consistent and even increased loss of potassium and phosphate as influenced by operation.

In the next group of patients, the same regimen was carried out except for the addition of 9 Gm of sodium chloride a day. Table II summarizes the urinary losses of 11 patients receiving daily intravenous infusions of 2 liters of 10 per cent glucose, each liter containing 4.5 Gm of sodium chloride. The individual variations are great, but the findings show a pattern of retention of sodium and chloride similar in each patient. This is shown especially by the graphic representation (Fig 4) in the five patients who underwent an uncomplicated cholecystectomy. For the first 24 hour post-operative period 76 per cent of the sodium injected and 70 per cent of the

TABLE II—*Postoperative Output in Urine Per 24 Hours*
Daily Intake 2000 cc 10 Per Cent Glucose in One Half Isotonic Saline

Case	Age Sex	Op	Postoperative 24 Hour Periods																Cumulative Balance							
			1				2				3				4				Na	K	Cl	N				
			Na	K	Cl	P	Na	K	Cl	P	Na	K	Cl	P	Na	K	Cl	P								
1	51F	GB	33	25	39	18	2	146	94	150	100	9	134	10	132	18	7	90	6	89	27	4	+209	-134	+205	-22
2	59F	GB	21	8	20	32	4	39	14	33	21	7	190	13	157	12	7	131	8	90	9	9	+234	-42	+318	-26
3	53F	GB	31	17	41	17	2	26	11	61	26	3														
4	46F	GB	23	12	27	8	1	139	60	154	42	7	125	26	145	11	5	63	22	103	36	4	+266	-120	+185	-17
5	48F	CO*	50	27	53	39	3	94	42	185	13	9	151	32	154	6	7	131	27	167	6	5	+190	-128	+138	-24
6	58F	AP*	54	44	72	17	5	75	26	90	4	7	116	16	151	16	6	108	10	127	1	4	+362	-97	+313	-23
7	71F	SR*	25	28	48	24	4	132	30	129	32	7	165	23	169	8	6	91	19	109	6	5	+139	-100	+84	-21
8	53F	TC	97	31	99	15	9	129	31	146	16	11	185	7	191	13	6	199	15	212	13	5	+6	-83	-34	-32
9	46F	EL*	102	52	160	38	6	56	25	68	27	4	139	21	153	14	4	170	18	169		4	+162	-116	+64	-18
10	71F	GR*	27	24	25	28	2	101	75	77	32	11	137	54	93	23	8	108	15	70	6	7	+207	-168	+351	-28
11	44F	GB	75	75	103	38	5	126	49	145	37	6	149	30	140	6	5	73	11	80	4	3	+192	-165	+149	-19

*Key Same as in Table III

chloride was retained. Of the total 9 Gm of sodium infused during the first 24 hour period, this represents a retention of nearly 7 Gm of NaCl. Retention of both Na and Cl continue during the second 24 hour period and during the third 24 hour period the excretion of sodium and chloride approaches the intake. The cumulative retention of Na and Cl for the 96 hour study period averages 39 per cent for Na and 37 per cent for Cl. This is equivalent to a retention of about 14 Gm of the 36 Gm of sodium chloride infused over the 96 hour period. The cumulative loss of K averaged 110.7 meq and of HPO_4 98.5 meq.

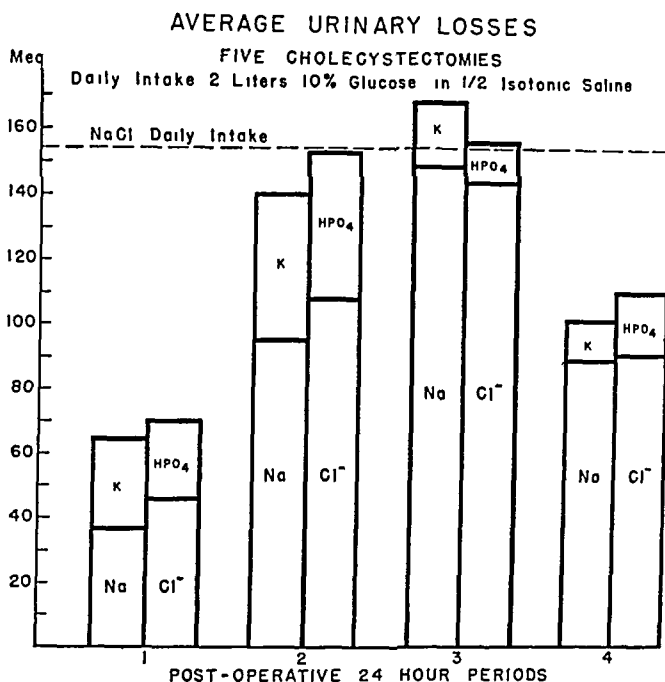


FIG 4—These patients received 9 Gm of salt each day, equally divided between the 2 liters of 10 per cent glucose. Note the retention of sodium and chloride ion most marked on the first day and then decreasing. Calculation of the averages in this group showed that about 40 per cent of the injected sodium chloride was retained by the body. Note on the other hand the consistent losses of potassium and phosphate, which indeed were greater on the second than the first day.

In order to show the influence of preoperative intake, the data on one patient, a 42-year-old female who underwent an uncomplicated cholecystectomy is shown in Figure 5. She was given 2 liters of 10 per cent glucose and 9 Gm of sodium chloride both before and after operation. This patient was ill prior to her admission to the hospital and had not been eating normally, but had not vomited. Note the retention of both Na and Cl preoperatively. This is similar, though even more marked in degree than the postoperative retention of sodium chloride of the patients in Figure 4. After operation, however, there was a retention of only 24 per cent of the Na and

POSTOPERATIVE MAINTENANCE REQUIREMENTS

TABLE III—Postoperative Output in Urine Per 24 Hours
Daily Intake 2000 cc 5 Per Cent Glucose in II ater

Case	Age Sex	Op	Postoperative 24 Hour Periods															Cumulative Loss								
			1					2					3						4							
			Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	P	N		Na	K	Cl	P	N			
1	36F	GB	10	8	13	6	1	37	43	77	31	5	3	21	32	14	4	6	10	14	16	3	55	82	135	13
2	61F	GB	28	25	74	22	2	49	96	55	9	11	8	23	23	4	7	1	5	20	11	7	86	149	170	27
3	16F	GB	21	45	46	40	5	26	37	65	30	8	12	19	27	12	5	5	13	15	15	6	63	112	152	25
4	23F	GB	3	28	13	34	7	1	11	0	14	5	5	9	7											
5	61F	EL	19	59	16	70	8	18	27	8	45	11	35	25	28	34	8	9	17	8	23	7	45	135	59	34
6	67F	AP*	9	5	15	34	5	7	25	21	26	8	6	15	32	23	7						22	44	114	21
7	35M	DL	40	111	70	90	11	3	13	14	17	5	7	12	11	21	6	6	34	17	5	14	56	172	116	35
8	36F	GB	88	65	134	5	6	69	37	57	1	8	13	17	18	1	5	10	16	18	3	6	179	135	181	25

Key

All values expressed as milliequivalents except nitrogen (N) which is expressed as grams

*—Patients given blood at operation

- GB—Cholecystectomy
- GR—Gastric Resection
- JL—Jejunostomy
- HY—Hysterectomy
- RM—Radical Mastectomy
- HI—Incisional Herniotomy
- TH—Thyroidectomy
- EL—Exploratory Laparotomy
- CO—Colectomy
- AP—Abdominal Perineal Resection
- SR—Sigmoid Resection
- TC—Transverse Colostomy

4 per cent of the Cl infused during the first 24 hour period, which is much lower than average. The output of NaCl approached the intake during the third day. The cumulative retention at the end of seven days of study, during which the same intake was given each day entirely by vein, was 125 meq of Na and 159 meq of Cl. This is equivalent to a retention of roughly 12 per cent of the sodium and 15 per cent of the chloride, or in grams, a retention of only 7 to 9 Gm of the 63 Gm of NaCl infused during this period, much less than the average as previously noted.

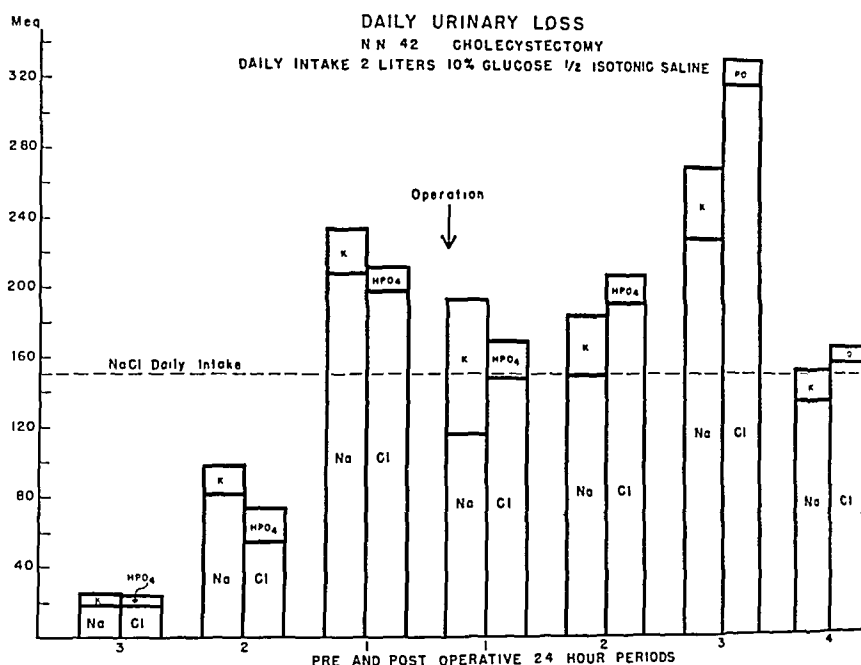


FIG 5—This patient received the same amount (9 Gm) of NaCl both before and after operation. Note that there was an even greater degree of retention of sodium chloride before operation as compared with the findings in Figure 4, presumably due to the fact that the patient took very little but water before this preoperative period of observation. Note also that the degree of retention after operation was less pronounced than in the case shown in Figure 4, thus illustrating the influence of previous salt intake.

The effect of a reduction in intake of glucose on electrolyte behavior is shown in Table III. This summarizes the electrolyte and nitrogen losses of eight patients receiving by daily intravenous injection 100 Gm of glucose, i.e., 2 liters of 5 per cent glucose in water. The 96 hour cumulative losses are fairly small (Na 88 meq, K 108 meq, Cl 144 meq, HPO₄ 63 meq, and N 22.4 Gm), but somewhat greater on an average than those patients receiving 200 Gm of glucose. Moreover, these losses were similarly accompanied by no significant changes in the blood levels of these electrolytes nor by any significant alteration in the CO₂ combining power, serum proteins or hematocrit (Table IV).

Glucose—The findings in regard to glucose concern the observed differences between an intake of 100 Gm and one of 200 Gm. First of all are the

POSTOPERATIVE MAINTENANCE REQUIREMENTS

TABLE IV—Pre- and Postoperative Blood Chemical Measurements

		Pre operative Blood										Post operative Blood									
		Intake/Liters																			
MC	Cholecystectomy	2 0 10% 1/2ISS	108 0	63 5	145 0	4 61	5 22	2 68	7 90	15	43 8	99 5	65 5	142 5	4 30	5 50	3 05	8 20	17	42 4	
DR	Cholecystectomy	2 0 10% 1/2ISS	92 0		137 0	2 55	4 50	3 00	7 50		42 8	100 5	75 5	146 7	3 00	3 86	3 29	7 15	28	38 8	
FL	Cholecystectomy	2 0 10% 1/2ISS	114 6	57 8	140 0	4 30	4 95	2 85	7 80	17	42 6	118 0	65 8	137 5	3 38	4 17	2 78	6 95	16	36 9	
EP	Cholecystectomy	2 0 10% 1/2ISS	116 0	64 0	148 5	3 78	4 78	2 42	7 20	19	48 0		63 1	150 0	3 65	3 70	2 60	6 30	17	42 0	
LR	Ileo Sigmoidostomy	2 0 10% 1/2ISS	102 5	61 1	140 5	3 72	5 49	3 21	8 70	12	44 4	120 0	70 6								
AF	Abd Peri Res	2 0 10% 1/2ISS	107 5	63 3	142 0	4 00	5 85	3 95	9 80	21	44 3	103 0	62 9	141 3	3 70	5 23	3 37	8 60	16	39 5	
LA	Res Primary Anast	2 0 10% 1/2ISS	111 0	70 0	135 0	4 80	4 49	3 66	8 15	21	44 0	105 0		140 6	4 56	3 57	3 82	7 40	38	0	
EG	Trans Colostomy	2 0 10% 1/2ISS	116 0	69 9	145 0	3 67	4 56	2 19	6 75	29	44 0	110 0	74 0	139 0	3 26	3 90	2 75	6 65	21	44 0	
FH	Gastrostomy Exp Lap	2 0 10% 1/2ISS	118 0	60 7	146 0	4 40	4 35	2 45	6 80	25	44 0	110 0		147 1	3 66	3 86	2 04	5 90	13	39 0	
CM	Subtotal Gastrectomy	2 0 10% 1/2ISS	123 0	71 3	140 5	4 95	3 19	2 19	5 38	31	41 0	117 0									
NN	Cholecystectomy	2 0 10% 1/2ISS	120 0	57 8	151 0	3 36	4 64	2 76	7 40	13	38 0	116 0	72 6	146 0	3 59	4 21	2 61	6 85	36	0	
MS	Colectomy Trans	2 0 10% 1/2ISS	88 0	61 5	138 9	4 04	5 17	2 08	7 25	17	36 0	121 0	71 7	148 0	3 96	4 17	2 68	2 85	23	41 7	
PB	Cholecystectomy	2 0 10% HOH	111 0	59 0	145 0	6 00	5 10	1 90	7 00	15	41 0	106 0	55 6	141 0	5 05	4 60	2 30	6 9	14	39 0	
MG	Cholecystectomy	2 0 10% HOH	102 5																		
MP	Cholecystectomy	2 0 10% HOH	104 3	51 9	140 5	4 73	4 47	3 53	8 00	31	48 6	88 0	56 7	131 0	4 55	4 41	3 69	8 1	25	47 7	
FH	Cholecystectomy	2 0 10% HOH	108 0	16 1	145 0	5 90	5 90	3 50	9 40	25	44 5	98 0	69 5	135 1	6 01	4 48	3 62	8 1	25	47 7	
EH	Cholecystectomy	2 0 10% HOH	110 7	67 6	137 3	5 62	4 86	2 09	6 95	32	37 0	98 0		136 2	5 00	4 16	2 99	7 15	40	0	
DH	Cholecystectomy	2 0 10% HOH	103 0	69 8	134 0	4 23	4 95	4 25	9 20	18	40 9	95 0	76 7								
CV	Gastric Resection	2 0 10% HOH	104 0	61 6	136 8	4 24	5 24	3 26	8 50	15	34 0	98 5	66 6	137 5	3 70	5 60	3 10	8 7	18	33 0	
WP	Gastric Resection	2 0 10% HOH	106 5	66 9	132 4	4 25	3 68	7 67	6 35	19	40 0	96 5	65 0								
MC	Abd Pan Hysterectomy	2 0 10% HOH	101 5	66 0	140 2	4 24	5 16	3 84	9 00	21	34 4	98 5	60 6	133 0	4 00	4 95	2 75	8 35	20	43 3	
FW	Abd Hysterectomy	2 0 10% HOH	102 5	28 8	138 0	4 53	5 23	3 47	8 70	17	37 6	97 5	59 5	132 2	3 85	5 72	3 38	9 1	24	31 2	
DO	Hysterectomy	2 0 10% HOH	107 5	58 5	136 5	5 30	4 94	3 66	8 60	17	34 9	101 5	65 4	142 0	4 13	4 48	3 52	8 0	20	31 6	
NH	Abd Pan Hysterectomy	2 0 10% HOH	110 0	60 5	145 0	6 72	5 85	2 75	8 60	18	48 0	106 0	61 9	136 2	5 90	5 34	2 76	8 1	22	48 9	
MP	Abd Pan Hysterectomy	2 0 10% HOH	105 2	55 7	143 7	5 60	4 63	2 42	7 10	14	48 0	106 0	55 0	144 0	5 68	4 90	3 60	8 5	17	46 0	
RD	Hysterectomy									24	30 0	101 0	55 0	138 5	5 10	4 80	2 40	7 2	24	38 8	
KR	Inc Hernia Repair																				
HH	Thyroidectomy																				
BB	Exp Laparotomy																				
All patients received 10% glucose in water (HOH) or in half strength isotonic saline (1/2 ISS)																					
Key All measurements of Cl CO ₂ Na and K were made in plasma and expressed as meq/liter																					
A G T refer to Albumin Globulin and Total Proteins in Plasma expressed in Gm per cent																					
NPN refers to nonprotein nitrogen of plasma as mg%																					
Hcrit is the hematocrit value expressed as a percentage of the whole blood volume																					

All patients received 10% glucose in water (HOH) or in half strength isotonic saline (1/2 ISS).
Key: All measurements of Cl CO₂ Na and K were made in plasma and expressed as meq/liter
A G T refer to Albumin Globulin and Total Proteins in Plasma expressed in Gm per cent
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Hcrit is the hematocrit value expressed as a percentage of the whole blood volume

nitrogen losses These were surprisingly low in both groups (Tables I, II and III) On an average, but 20 to 25 Gm of nitrogen were lost during the entire four day postoperative period or about 4 to 5 Gm a day Only two specimens contain more than 20 Gm, one on the third day following a gastric resection, the other on the third day following hysterectomy Only 17 specimens of the nearly 160 examined contained 10 Gm or more of nitrogen Moreover, comparison of the nitrogen loss in patients receiving 100 with those receiving 200 Gm of glucose reveal little difference, i e, 26 as compared with 23 Gm for the average total 96 hours Scrutiny of the individual cases also reveals no significant difference

In all three groups, glycosuria and acetonuria were observed (See Table V) Of eight patients receiving daily intravenous infusions of 2 liter-

TABLE V—*Glycosuria and Acetonuria Following Operation*
Daily Intake 2000 cc per 24 Hours

	I 5% Glucose (100 Gm) in Water	II 10% Glucose (200 Gm) in Water	III 10% Glucose (200 Gm) in $\frac{1}{2}$ Isotonic Saline
Number patients studied	8	10	11
Patients showing glycosuria	6	10	11
Average amount glucose spilled (Gms)	12.9	18.4	34.1
Range in amount glucose spilled (Gms)	2.2—24.3	1.5—88.0	6.1—82.8
Av rate of infused glucose in Gms/kg body wt/hr	23	48	52
Patients showing acetonuria	6	2	6
Number 24 hour urine collections examined	31	37	39
24 hour urine collections containing acetone (%)	52	5	21
24 hour urine collections containing glucose (%)	42	86	92
Av cumulative 96 hour urinary Na loss (meq)	72	87	(197)*
Av cumulative 96 hour urinary K loss (meq)	118	103	115
Av cumulative 96 hour urinary Cl loss (meq)	132	126	(177)*
Av cumulative 96 hour urinary P loss (meq)	1.82	1.27	1.28
Av cumulative 96 hour urinary N loss (Gms)	26	29	23

*This figure represents positive balance i e retention of the injected sodium chloride in this group

of 5 per cent glucose and water for four postoperative 24 hour periods, six had glycosuria at some time during this period and 42 per cent of the 24 hour urine specimens contained glucose The average amount was 13 Gm The range in degree of glycosuria varied from as little as 2.2 Gm of sugar to 24.3 Gm It should be emphasized, however, that the average rate of infusion was 0.23 Gm per Kg of body weight per hour As to acetonuria, six of these eight patients showed a positive test at some time during their postoperative period and 52 per cent of the 24 hour urine specimens contained from traces to 4 plus acetone Five of the six patients having acetonuria also showed glycosuria during the same 24 hour period on one or more occasions during the four days of study

Of the patients receiving daily infusions of 2 liters of 10 per cent glucose and water, 10 with and 11 without added electrolyte, all had glycosuria and

86 and 92 per cent of the 24 hour urine specimens contained glucose respectively. The average amount spilled was 18 and 34 Gm respectively, and the range varied from 1.5 to 88 Gm of glucose. It should be emphasized that the average rate of infusion was 0.48 and 0.54 Gm per Kg of body weight per hour, or twice that of those receiving 5 per cent glucose. Only eight of the 21 patients had acetonuria varying from traces to 2 plus, all eight patients at one time or another had acetonuria and glycosuria during the same 24 hour period. Only minor differences were discernible between those receiving 10 per cent glucose in water and those receiving 10 per cent glucose in saline.

DISCUSSION

The objective regarding minimum needs suggested in the title of this report has only been partly met by the evidence herein presented. Nevertheless, a few inferences may be drawn as to how little the postoperative patient may be given to maintain normal function. It should be mentioned at the outset however that such inferences are based upon the assumption that balance studies are valid as a guide to estimating such needs. This assumption has the sanction of general acceptance. Moreover, it is logical to believe that in the absence of deficits, intake of each element should balance the output just as energy intake equalizes energy expenditure. One of the possible pitfalls is the statement "in the absence of deficits," the truth of which may be difficult to establish in each individual patient. Another pitfall is the possibility that even in the absence of deficits some elements may be retained with physiological improvement, or that, vice versa, a "negative balance" may be beneficial because the body wishes to rid itself of an excess of a normal biochemical constituent. In spite of these and perhaps other objections, inferences will be based upon the validity of the idea that a balance of intake and output indicates an optimum physiological state.

The data on water balance seem to indicate that in the normally hydrated adult 2 liters is an adequate fluid intake in the absence of pathological losses. This is shown by the fact that this intake was accompanied by an adequate urinary output. Body weights, it is true, were not determined, and this would have given accurate confirmation as to the amount of insensible water losses. However, the average difference between intake and urinary output was about one liter, which is roughly that of the insensible loss. Thus it is likely that the fall in body weight would have been approximately one Kg per day plus whatever loss was due to an inadequate caloric or nitrogen intake. Thirst might be considered as a guide to the measure of water needs. As already mentioned, however, so many postoperative and post-traumatic patients experience thirst, even on a larger water intake, that its significance remains unestablished. The fact that blood studies showed no change in electrolyte concentration or hematocrit would seem to indicate that dehydration did not occur on this intake. Thus it would seem justified to infer that 2 liters are all that are necessary to maintain water balance in

the postoperative patient This agrees rather well with data obtained on normal humans subjected to starvation^{8, 10, 24}

The oliguria observed on the first postoperative day was not unexpected since it is a common clinical observation that patients seldom excrete as much urine during this period as they do later Of greater interest was the fall in the creatinine output with no change in specific gravity Since creatinine is cleared by the kidneys so readily, and concentrating function is performed by the tubules, it would seem that the oliguria was due to a decrease in the effective renal plasma flow and filtration fraction Further observations, however, are necessary to be sure that this was the correct explanation

The electrolyte needs may be partially estimated from the findings herein recorded It is true that the loss during an intake of water and glucose alone was not very great, and was accompanied by no fall in the electrolyte composition of the blood However, even small losses are probably not without some significance It would be a simple matter indeed to provide this intake by the addition of a few grams of sodium and potassium salts On the other hand, the addition of 9 Gm of sodium chloride seems too great inasmuch as there was a retention averaging about 40 per cent of that injected The degree of retention is certainly greatly influenced by the previous intake, i.e., the lower the intake before operation the greater the degree of retention This is due to a fairly well known lag in the ability of the human kidney to excrete salt above the previous level of intake This is true under normal conditions of oral intake as shown by White and Findley,²² and is especially true after operation as shown by Stewart and Rourke¹⁸ and others Whether operative or accidental trauma and anesthesia increase this lag cannot be inferred from the present data Further studies with careful comparison of pre- and postoperative retention is needed In any case, it would seem, on the basis of the present observations with a daily intake of 9 Gm of NaCl, that 4 Gm would probably not lead to retention On the basis of the much smaller sodium chloride losses on no intake, a balance may be struck, indicating that an average of between 2 and 4 Gm of sodium chloride a day would probably produce balance in the average patient The need for adding potassium rests on the assumption that losses in this element should be replaced On such a basis about one to 2 Gm of potassium salt should be added to the daily intake If both salts were added as the chloride, a much larger amount of chloride would be present than seems to be needed on the basis of the present findings Cations can readily be added without anions in the form of sodium or potassium lactate or gluconate This does not take into account other electrolytes such as magnesium and perhaps the anions sulfate and phosphate Further observations will be needed before their requirements can be definitely established

It must be admitted, of course, that for short periods of time it is unlikely that serious physiological impairment will follow small deficits in these electrolytes, such as might follow their deprivation Thus it might be

argued that simple fluids without salt might be adopted as routine. The difficulty with this point of view is that one never knows when the parenteral route may be required for longer than a few days. Furthermore, exact replacement, while not always essential, is a better basis for therapy than conclusions drawn from the results of experience alone. Further observations are being made in order to determine more accurately what pattern of electrolyte intake will lead to balance under normal conditions.

Findings in regard to glucose needs may be discussed in two parts. First is its sparing effect on tissue protein breakdown. As will be noted, the tissue protein loss as measured by the nitrogen excretion in the urine was surprisingly low in all of the cases studied, indicating that in these instances at least there was very little catabolic reaction, a finding which is contrary to many we have previously made and which have been made by others^{4, 5}. It is, therefore, not surprising that there was very little difference in the nitrogen loss when the glucose intake was 200 Gm. as compared with 100 Gm. This would seem to confirm the finding of Gamble¹⁰ that in normal human beings an intake of 100 Gm. of glucose a day produces the maximum sparing effect on tissue protein breakdown, and that an increase to 200 Gm. does not decrease the tissue protein loss. It should be mentioned, however, that in the present observations a variable amount of glucose was lost in the urine, and that this loss was greater in those receiving 200 Gm. Thus the effective amount of glucose available for metabolic needs was much less than 200 Gm. and indeed in one case, was only about a little over 100 Gm. It seems unlikely, however, that even with full utilization of the entire 200 Gm. further reduction in the low nitrogen loss could be effected.

The second finding concerns the degree of glycosuria and acetonuria observed. Glycosuria and acetonuria were noted in a large percentage of the cases studied. Since the rate of injection even with the 10 per cent solution was fairly low, i.e., 0.52 Gm. per Kg. per hour, the appearance of glycosuria must be taken as an indication that the postoperative patient operated under gas-oxygen-ether anesthesia under the present circumstances cannot utilize glucose as well as the normal¹⁴. Even when the rate was half this, i.e., 0.25 Gm. per Kg. per hour, as was the case with the 5 per cent solution, sugar was still spilled in the urine. It is probable that this glycosuria might have been avoided if the injection had been started at a slower rate in accordance with the Staub effect, as reported by Pareira and Somogyi¹⁵.

Acetone in the urine occurred more frequently when 5 per cent glucose was given than when 10 per cent glucose was injected. Pareira and Somogyi¹⁵ observed ketonuria in a postoperative patient during the injection of 5 per cent glucose, which disappeared with a change to 10 per cent glucose. We have no data as to the exact significance of this finding inasmuch as 24 hour urine specimens only were measured. The appearance of a small amount of acetone during even one or two hours of the total 24 hour period, while of

little significance, would give a positive result. Nevertheless, it must be admitted that even a small amount of acetone in the urine under these conditions means that at some interval of time during the 24 hours the liver was probably free of glycogen, or that ketone bodies were being produced more rapidly than they could be utilized.

From the findings herein presented and from other considerations, it would seem safe to conclude that a full caloric quota by the injection of 4 liters of 10 per cent glucose is not ordinarily necessary nor indeed desirable. First it would probably not spare any more tissue protein, and in fact merely would spare the breakdown of tissue fat. Moreover, it is unlikely that, without special control of the rate of injection, all of this amount could be utilized by the body after operation, but that much of it would appear in the urine. Finally, the mechanical problem of administering this much glucose would seem too great to be justified. Nevertheless, the appearance of acetonuria on the lower intakes deserves careful scrutiny. The claim of Pereira and Somogyi¹⁵ that up to 350 Gm spaced over the entire 24 hour period is needed to avoid ketosis suggests the need for further study of this question.

Glucose utilization is, of course, influenced by many factors, and it is probable that the use of gas-oxygen-ether anesthesia plays an important role. For example, it is likely that the same operative procedures carried out under spinal anesthesia might provoke much less glycosuria and acetonuria. The mechanism of these disturbances in carbohydrate metabolism as herein observed deserves further investigation.

The significance of the potassium losses may be discussed in terms of protein losses. This is usually done by establishing a K/N ratio based upon computing the potassium loss in millimols and the nitrogen loss in grams. This has been calculated in 26 of the patients observed in this study. Only six of them showed a value below three, and in most of them the figure was between four and six. A ratio of three or less is considered by most authorities to represent the normal relationship of intracellular potassium to protein. Our findings, therefore, suggest that the destruction of the patient's protoplasm was not the sole source of the potassium loss, and that much of it originated in another way, perhaps by loss of cell potassium without loss of protoplasm.

SUMMARY

1. Balance studies were carried out in 40 surgical patients on a completely intravenous intake for 96 postoperative hours, and in a few cases during several preoperative days. Study of the urinary output included volume, specific gravity, creatinine, sodium, potassium, chloride, phosphate, nitrogen, glucose and acetone. Blood levels of sodium and potassium chloride, CO_2 , plasma protein and red cell volume were also measured before and after each study.

2 With an intake limited to 2 liters a day there was an adequate urinary output during the four postoperative days of about one liter except for a moderate oliguria during the first postoperative day. The oliguria was accompanied by a decreased creatinine excretion with no change in specific gravity.

3 With no electrolyte intake, the body rapidly conserves sodium and chloride, but not potassium and phosphate. The cumulative loss during four postoperative days averaged about 4 Gm calculated as sodium chloride and 6 Gm calculated as potassium chloride. No changes in plasma levels of sodium, potassium, CO₂, proteins or in red cell volume were observed on this intake.

4 With an intake of 9 Gm of sodium chloride a day, there was a definite lag in excretion so that of the 36 Gm injected, an average of about 14 Gm was retained. The loss of potassium, however, was the same.

5 It is estimated from these findings that an intake of 2 liters of water plus 2 to 4 Gm of a mixture of sodium and potassium chloride (or gluconate) would meet the minimum requirements for these elements in the postoperative patient.

6 Calculation of the potassium-nitrogen excretion ratio suggests that only part of the potassium loss originated from the breakdown of tissue protoplasm.

7 The nitrogen sparing effect of 200 Gm of glucose was not significantly greater than 100 Gm of glucose. On the other hand, because of an undoubted disturbance in carbohydrate metabolism, acetonuria was more frequent under the latter than under the former intake. Glycosuria conversely was greater with a 200 Gm intake as compared with a 100 Gm intake. In order to determine the minimum requirements for glucose, further observations will be necessary, particularly with regard to the influence of the rate of injection.

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DISCUSSION—DR ROBERT ELMAN, St Louis, Mo In spite of the published warnings of Dr Collier and many others, it has been my observation that too much intravenous fluid is still being given in many hospitals I would include in this plasma and whole blood transfusions

Not only are many of these injections costly and inconvenient, but are too often actually or potentially dangerous Whenever we use this method of therapy, we therefore have the responsibility of knowing exactly the specific amounts of each element needed for maintaining normal physiological activity

It was largely for this reason that we are making this preliminary report of the minimum parenteral requirements in patients who for one reason or another take nothing by mouth I might say that the 96-hour period of observation we used was purely experimental I don't want to leave the impression that all of our gallbladder patients required parenteral injections during such a long period

Our objective could be expressed by a very simple dictum, that is, the use of better but less parenteral fluids

On the basis of the present findings we believe that 2 liters of water and perhaps even a little less in the normal hydrated adult will meet these minimum requirements for water under conditions of the present study

As to salt intake, we have confirmed the observations of Dr Lester White, our professor of physiology, and others, that the normal human kidney lags in its excretion for several days whenever presented with salt above the previous level of intake Since surgical patients often are on simple liquids before operation—and I am excluding those with salt losses due to vomiting, and so on—it is clear that their kidneys may not be able to excrete much salt, so that more will be retained than those on a normal intake up to 9 Gm a day

This behavior of the human kidney is quite unlike that of the dog, which excretes added loads of salt rapidly This difference is one reason among others for the pitfalls which may come from translating data on animals to human beings

Finally, I would like to point out that our findings on the disturbed utilization of sugar after operation, while perhaps not surprising, may be decisively influenced by the addition of amino acids, a factor which we are now studying separately This is based upon a few observations made already, which indicate that the addition of amino acids to intravenous glucose in normal humans, at least, seems to increase the utilization of glucose by the tissues

THE METABOLIC FATE OF THE INFUSED ERYTHROCYTE*

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INTRODUCTION

IN RECENT YEARS, there has been considerable interest in the nutritional problems of surgical patients. In particular, nitrogen metabolism has been extensively studied, and it has become increasingly apparent that most seriously ill patients require amounts of nitrogen far above the needs of normal individuals. Most of these same patients receive many blood transfusions, and the question arises "To what extent do these transfusions contribute to the patients' nutritional requirements?" In particular, should the infused red cell nitrogen which quantitatively is two to three times greater than the associated plasma nitrogen, be included as intake in day to day balance studies?

At present no consistent policy has been adopted in this regard, some investigators¹⁻³ including the red cell nitrogen as intake, others not⁴. Where such nitrogen has been included in calculations of daily balance, apparent positive nitrogen balance has been readily attained, and the catabolic phase following injury has apparently been reversed. Other workers, in studies of similar patients, in which, however, the red cell nitrogen was not counted as a source of available nitrogen in the calculation of daily balances, were unable to reverse the negative nitrogen balance following injury. Clearly, such conflicting descriptions of results from similar studies indicate a clouded notion of the exact role played in the body metabolism by the infused erythrocyte. Actually, there has been relatively little quantitative data available on which to base a considered opinion. To clarify this situation, the present study was undertaken.

METHODS

Two adult, male medical students, healthy and ambulant, were boarded on the metabolic ward at the University of Illinois Research and Educational Hospital. They were each maintained throughout the period of nitrogen balance study on a five-day rotating dietary schedule. The diets were composed of natural foodstuffs and amounted to 0.75 Gm protein and 45 calories per Kg body weight daily. Fluid intake was not restricted. Activities, although not restricted to any absolute schedule, were relatively constant from day to

* Read before the American Surgical Association, St. Louis, Mo., April 22, 1940. The opinions expressed in this paper do not necessarily represent the official views of any governmental agency.

day Body weights were recorded daily Following a control period of about one month, fresh, separated red cells (drawn from male donors on the day of infusion),[†] resuspended in isotonic saline just before administration, were injected into each of the two subjects for two and three days, respectively The subjects were group O, Rh-, MN Group O, Rh- red cells were infused and one transfusion in each series was made up of N cells It was, therefore, possible to differentiate between the recipient and representative donor cells, and to quantitate, by the Ashby technic as modified by Ebert and Emerson,⁷ the percentage of each cell type circulating

Plasma volumes were measured by the T-1824 dye technic⁶ Total blood volumes and corrected circulating red cell masses were calculated from the observed dye plasma volumes and the venous hematocrits, applying the 0.85 correction suggested by Gibson *et al*⁷

Red and white blood cell counts, hemoglobins, hematocrits, and reticulocytes were determined by routine methods⁸

Nitrogen content of the food was calculated from standard tables,⁹ corroborated by spot, full-day analyses of each diet used Total nitrogen of food, infused cells, serum, urine and feces was determined by Ma and Zuazaga's¹⁰ modification of the micro-Kjeldahl method of Keys Urine was collected in two day periods, feces over five days (marked with carmine)

Serum NPN was measured by the method of Koch and McMeekin as modified by Daly¹¹ Howe's method¹² was used for the estimations of albumin and globulin Fecal urobilinogen was measured by the method of Terwen as modified by Watson¹³ The following liver function tests were performed bromsulfalein,¹⁴ thymol turbidity and flocculation,¹⁵ serum bilirubin, direct and total¹⁶

After the nitrogen balance studies were completed, the subjects were on diets of their own choice Determinations of plasma volume, red cell masses, and routine hematology were carried out at various intervals until complete disappearance of the infused cells

RESULTS

A Body Weight, Nitrogen Balance and Circulating Plasma Protein The data in regard to diet, body weight, nitrogen balance and circulating plasma protein are presented in Tables I, II, III, IV, and V, and Figs 1 and 2

Each subject was on a fixed dietary intake of 0.75 Gm protein and 45 calories per day This amounted to 8.1 Gm of nitrogen and 3020 calories for the first subject (MNL 1) and 8.8 Gm of nitrogen and 3315 calories for the second (MNL 2) Approximately 44 per cent of the calories came from protein There was minimal variation among the five serially rotated diets

On this regimen, body weights were maintained, and nitrogen excretions, both fecal and urinary, were essentially constant during the control periods (Tables II, III and Fig 1) One subject (MNL 2) was in minimal positive

† Prepared by The Michael Reese Serum Center

METABOLIC RATE OF INFUSED ERYTHROCYTE

nitrogen balance of 0.1 Gm per day, while the other (MNL 1) was in slightly more positive balance, 0.5 Gm nitrogen per day

After 26 and 18 days respectively, fresh, separated red cells were infused. Subject MNL 1 received approximately 225 cc cells daily for three days, subject MNL 2, approximately 250 cc daily for two days. In terms of red cell nitrogen, this amounted to a total of approximately 36 and 26 Gm respectively

TABLE I—Mean Daily Dietary Intake

Nutrient	Subject	
	MNL 1	MNL 2
Calories	3020	3315
Nitrogen (Gm)	8.1	8.8
Carbohydrate (Gm)	330	365
Fat (Gm)	165	180

NITROGEN DATA IN TWO NORMAL MALES MADE POLYCYTHEMIC BY ERYTHROCYTE INFUSIONS

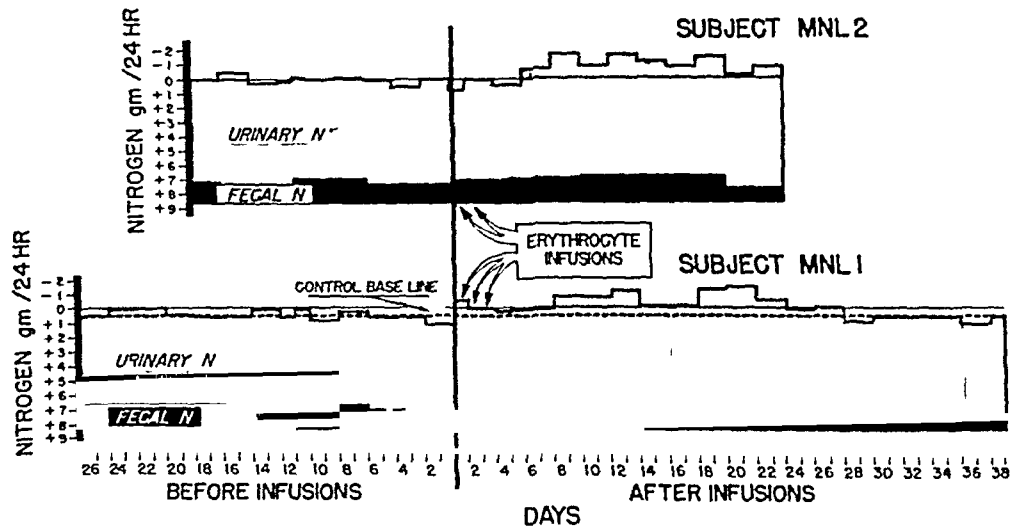


FIG 1—A slow steady excretion of “extra” nitrogen, over and above the preinfusion mean, follows the infusion of erythrocytes into normal males in amounts sufficient to produce a significant polycythemia. In the figure the nitrogen of the infused red cells is not charted as intake

Thus, on the days of infusions, the total nitrogen intake of each subject was more than doubled

Both subjects developed fever, malaise and the other evidences of an acute influenzal infection within 48 hours following the first red cell infusion. This persisted for two to three days, the highest temperature reached being about 102 degrees in each case. Neither subject was seriously ill. There was no evidence of any transfusion reactions

TABLE II—*Nitrogen Balance Data in a Normal Male Made Polycythemic by Erythrocyte Infusions*

Subject MNL 1—Nitrogen Intake 8.06 Gm Daily

Day of Study	Weight (Kg)	Urine Nitrogen (Gm)	Fecal Nitrogen (Gm)	Total Nitrogen Excretion (Gm)	Nitrogen Balance (Gm)	Extra Nitrogen Excretion Above Preinfusion Mean (Gm/day)	Extra Nitrogen Excretion Above Preinfusion Mean (Gm cumulative)
Before Infusion							
26	66.9	6.28	1.31	7.59	0.47		
25	67.0	6.28	1.31	7.59	0.47		
24	66.6	6.60	1.31	7.91	0.15		
23	66.4	6.60	1.31	7.91	0.15		
22	66.5	6.65	1.31	7.96	0.10		
21	66.7	6.65	1.34	7.99	0.07		
20	66.7	6.29	1.34	7.63	0.43		
19	66.6	6.29	1.34	7.63	0.43		
18	66.7	6.15	1.34	7.49	0.57		
17	66.6	6.15	1.34	7.49	0.57		
16	66.3	6.59	0.86	7.45	0.61		
15	66.5	6.59	0.86	7.45	0.61		
14	66.5	7.10	0.86	7.96	0.10		
13	66.5	7.10	0.86	7.96	0.10		
12	66.3	6.55	0.86	7.41	0.65		
11	66.4	6.55	1.38	7.93	0.13		
10	66.7	5.90	1.38	7.28	0.78		
9	66.0	5.90	1.38	7.28	0.78		
8	65.9	6.51	1.38	7.89	0.17		
7	66.5	6.51	1.38	7.89	0.17		
6	66.5	6.39	0.86	7.25	0.81		
5	66.2	6.39	0.86	7.25	0.81		
4	66.0	6.39	0.86	7.25	0.81		
3	66.1	6.39	0.86	7.25	0.81		
2	66.4	7.00	0.86	7.86	0.20		
1	66.4	7.00	0.86	7.86	0.20		
After Infusion							
1	66.4	7.48	1.09	8.57	-0.51	1.01	1.01
2	66.8	6.97	1.09	8.06	0.00	0.50	1.51
3	66.9	6.97	1.09	8.06	0.00	0.50	2.01
4	66.3	6.78	1.09	7.87	0.19	0.31	2.32
5	65.9	6.78	1.15	7.93	0.13	0.37	2.69
6	66.6	6.78	1.15	7.93	0.13	0.37	3.06
7	66.4	6.78	1.15	7.93	0.13	0.37	3.43
8	66.5	7.73	1.15	8.88	-0.82	1.32	4.75
9	67.2	7.73	1.15	8.88	-0.82	1.32	6.07
10	66.7	7.64	1.25	8.89	-0.83	1.33	7.40
11	66.7	7.64	1.25	8.89	-0.83	1.33	8.73
12	66.8	8.06	1.25	9.31	-1.25	1.75	10.48
13	66.5	8.06	1.25	9.31	-1.25	1.75	12.23
14	66.5	7.02	1.25	8.27	-0.21	0.71	12.94
15	66.5	7.02	1.31	8.33	-0.27	0.75	13.69
16	66.4	7.04	1.31	8.35	-0.29	0.77	14.46
17	66.5	7.04	1.31	8.35	-0.29	0.77	15.23
18	66.0	8.21	1.31	9.52	-1.46	1.96	17.19
19	66.4	8.21	1.31	9.52	-1.46	1.96	19.15
20	66.6	8.49	1.27	9.76	-1.70	2.20	21.35
21	65.9	8.49	1.27	9.76	-1.70	2.20	23.55
22	66.4	7.53	1.27	8.80	-0.74	1.24	24.79
23	66.2	7.53	1.27	8.80	-0.74	1.24	26.03
24	66.4	7.09	1.11	8.20	-0.14	0.64	26.67
25	65.8	7.09	1.11	8.20	-0.14	0.64	27.31
26	66.0	7.37	1.11	8.48	-0.42	0.92	28.23
27	65.8	7.37	1.11	8.48	-0.42	0.92	29.15
28	65.5	6.30	1.11	7.41	0.65	-0.15	29.00
29	66.0	6.30	1.07	7.37	0.69	-0.19	28.81
30	66.0	6.61	1.07	7.68	0.38	0.12	28.93
31	65.6	6.61	1.07	7.68	0.38	0.12	29.05
32	65.9	6.68	1.07	7.75	0.31	0.19	29.24
33	65.8	6.68	1.07	7.75	0.31	0.19	29.43
34	65.5	6.61	1.12	7.73	0.33	0.17	29.60
35	65.5	6.61	1.12	7.73	0.33	0.17	29.77
36	65.6	6.31	1.12	7.43	0.63	-0.13	29.64
37	65.6	6.31	1.12	7.43	0.63	-0.13	29.51
38	65.5	6.70	1.12	7.82	0.24	0.26	29.77

TABLE III—*Nitrogen Balance Data in a Normal Male Made Polycythemic by Erythrocyte Infusions*

Subject MNL 2—Nitrogen Intake 8.77 Gm Daily						Extra Nitrogen Excretion Above Preinfusion Mean (Gm /day)	Extra Nitrogen Excretion Above Preinfusion Mean (Gm cumulative)
Day of Study	Weight (Kg)	Urine Nitrogen (Gm)	Fecal Nitrogen (Gm)	Total Nitrogen Excretion (Gm)	Nitrogen Balance (Gm)		
Before Infusion							
18	72.6	7.11	1.61	8.72	0.05		
17	72.0	7.11	1.61	8.72	0.05		
16	71.6	7.83	1.51	9.34	-0.57		
15	71.2	7.83	1.51	9.34	-0.57		
14	70.7	7.06	1.51	8.57	0.20		
13	70.7	7.06	1.51	8.57	0.20		
12	71.2	7.10	1.51	8.61	0.16		
11	70.7	7.10	1.75	8.85	-0.08		
10	70.2	6.92	1.75	8.67	0.11		
9	70.3	6.92	1.75	8.67	0.11		
8	70.5	7.00	1.75	8.75	0.02		
7	70.7	7.00	1.75	8.75	0.02		
6	70.7	7.30	1.30	8.60	0.17		
5	70.4	7.30	1.30	8.60	0.17		
4	70.0	6.82	1.30	8.12	0.65		
3	70.1	6.82	1.30	8.12	0.65		
2	70.3	7.34	1.30	8.64	0.13		
1	69.9	7.34	1.30	8.64	0.13		
After Infusion							
1	70.2	6.24	1.61	7.85	0.92		
2	71.0	7.01	1.61	8.62	0.15		
3	72.0	7.01	1.61	8.62	0.15		
4	71.7	6.62	1.61	8.23	0.54		
5	71.2	6.62	1.64	8.26	0.51		
6	71.0	7.76	1.64	9.40	-0.63	0.73	0.73
7	70.0	7.76	1.64	9.40	-0.63	0.73	1.46
8	70.5	8.67	1.64	10.31	-1.54	1.64	3.07
9	70.4	8.67	1.64	10.31	-1.54	1.64	4.70
10	69.7	7.68	1.75	9.43	-0.66	0.76	5.45
11	69.8	7.68	1.75	9.43	-0.66	0.76	6.20
12	69.9	8.46	1.75	10.21	-1.44	1.54	7.73
13	69.7	8.46	1.75	10.21	-1.44	1.54	9.26
14	69.3	7.92	1.75	9.67	-0.90	1.00	10.25
15	69.6	7.92	1.75	9.67	-0.90	1.00	11.24
16	69.4	7.62	1.75	9.37	-0.60	0.70	11.93
17	69.9	7.62	1.75	9.37	-0.60	0.70	12.62
18	69.7	8.25	1.75	10.00	-1.23	1.33	13.94
19	69.4	8.25	1.75	10.00	-1.23	1.33	15.26
20	68.9	7.79	1.01	8.80	-0.03	0.13	15.38
21	69.2	7.79	1.01	8.80	-0.03	0.13	15.50
22	69.8	8.29	1.01	9.30	-0.53	0.63	16.12
23	70.1	8.29	1.01	9.30	-0.53	0.63	16.74

Beginning at once after the infusions in subject MNL 1, and after a few days in subject MNL 2, "extra" nitrogen, 0.5 to 1.0 Gm daily over and above the preinjection control mean values, appeared in the urine (Tables II and III and Fig 1). Fecal nitrogen was unchanged. The increased urinary nitrogen excretion persisted throughout the period of observation (23 days post-infusion) in subject MNL 2. Subject MNL 1 was followed for a longer period of time, and the "extra" urinary nitrogen excretion lasted for about one month. Thereafter, nitrogen excretion became stabilized at the preinjection level.

TABLE IV—*Nitrogen Excretion in Normal Males Made Polycythemic by Erythrocyte Infusions*

(Extra nitrogen Excretion Above Pre infusion Mean cumulative expressed as per cent of infused erythrocyte nitrogen)

Day of Study After Infusions	Subject	
	MNL 1	MNL 2
1	2.8	0
2	4.2	0
3	5.6	0
4	6.4	0
5	7.5	0
6	8.5	2.8
7	9.5	5.6
8	13	12
9	17	18
10	21	21
11	24	24
12	29	30
13	34	36
14	36	40
15	38	43
16	40	46
17	42	48
18	48	57
19	53	59
20	59	60
21	66	61
22	69	62
23	73	64
24	74	
25	76	
26	78	
27	81	

In Fig 2 and Table IV the "extra" urinary nitrogen, expressed as per cent of the infused red cell nitrogen, is listed cumulatively. It is apparent that although the subjects received different quantities of red cells, and excreted different absolute amounts of excess nitrogen, the excretion was proportionately the same. By the time the preinjection urinary nitrogen level was reached, "extra" nitrogen *mathematically equivalent to (but not necessarily derived from)* 80 per cent of the infused red cell nitrogen had been excreted.

The total circulating plasma proteins (Table V) remained essentially unchanged throughout the control and experimental periods.

NITROGEN EXCRETION IN NORMAL MALES MADE POLYCYTHEMIC BY ERYTHROCYTE INFUSIONS

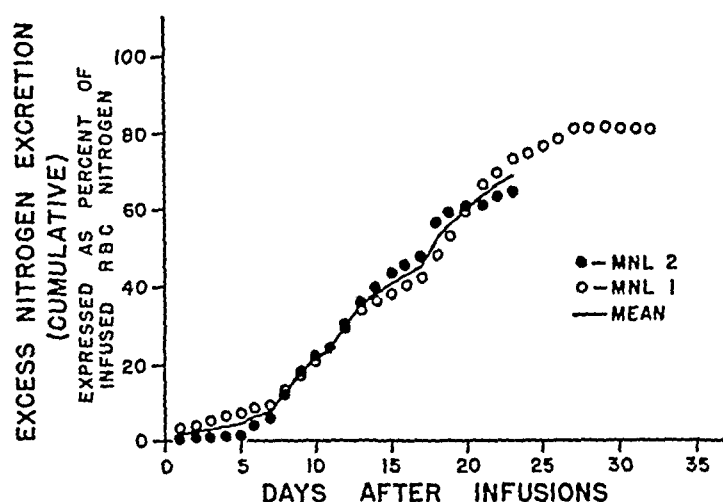


FIG 2—It is apparent that the quantities of "extra" nitrogen excreted following erythrocyte infusions in normal males is proportional to the quantity of red cell nitrogen infused

TABLE V—Total Serum Protein, Albumin and Globulin in Normal Males Made Polycythemic by Erythrocyte Infusions

Day of Study	Total Protein (Gm /100 ml serum)	Albumin (Gm /100 ml serum)	Globulin (Gm /100 ml serum)	Total Circulating Serum Protein (Gm)	Total Circulating Serum Albumin (Gm)	Total Circulating Globulin (Gm)
Subject MNL 1						
Before Infusion						
17	6 5	4 4	2 1	190	130	61
6	6 6	4 5	2 1	195	130	60
After Infusion						
8	6 1	4 1	2 0			
16	6 6	3 9	2 7	190	110	77
22	6 6	4 7	1 9	185	130	53
51	6 2	4 4	1 8	190	135	55
87	5 9	4 1	1 8	190	130	58
108	6 7	4 4	2 3			
Subject MNL 2						
Before Infusion						
6	6 3	4 2	2 7	225	150	96
3	6 0	3 9	2 1	215	140	75
After Infusion						
8	6 3	3 7	2 6	225	130	93
16	6 1	4 1	2 0			
22	6 3	4 1	2 2	230	150	80
48	6 1	4 1	2 0	235	160	78
86	6 2	4 2	2 3	225	155	85
107	6 1	4 2	1 9	215	150	68

B Plasma Volume, Red Cell Mass, Erythrocyte Survival and Production In order to follow erythrocyte survival, serologically identifiable red cells had been infused. It was therefore possible to differentiate between representative donor and recipient cells, and to quantitate the number of each cell type circulating.

In Fig 3 and Table VI plasma volumes, red cell masses, and survival of the donor and recipient cells in subject MNL 1 are plotted. There were no significant changes in plasma volume throughout the period of study. Following the infusions, there was a progressive fall in the initially increased red cell

TABLE VI—*Plasma Volumes, Hematocrits and Red Cell Masses in Normal Males Made Polycythemic by Infusions of Erythrocytes*

Day of Study	Plasma Volume (ml)	Hematocrit %	Total Red Cell Mass (ml)	Subject's Own Red Cell Mass (ml)	Infused Red Cell Mass (ml)
Subject MNL 1					
Before Infusion					
17	2860	43	1800	1800	0
6	2985	42	1820	1820	0
After Infusion					
3	2930		2485	1810	675
16	2860	51	2535	1960	575
22	2780	47	2175	1625	550
38	3195	40	1810	1310	500
51	3070	41	1800	1430	370
87	3205	40	1835	1725	110
Subject MNL 2					
Before Infusion					
6	3700	46	2695	2695	0
3	3450	47	2600	2600	0
After Infusion					
3	3575	51	3150	2650	500
8	3570	51	3180	2675	505
48	3875	43	2465	2165	300
86	3700	44	2450	2220	230
107	3510	44	2400	2300	100
127		48			0

mass, and, by the 38th day it had returned to the preinjection level. The hematocrit had also returned to normal by this time. Although the hematocrit and red cell mass had returned to the preinjection levels, this was not due to an increased destruction rate of the infused cells but rather to a concomitant decrease in the recipient's own cells. Thus, while the subject's own red cell mass was about 1800 ml during the control period, it was only about 1300 ml at the 38th day post infusion.

As may be seen in the lower half of Fig 3, the observed survival of the infused cells followed the theoretical line of a normal rate of 0.8 per cent

C Liver Function In Table VII and Figs 6 and 7 are plotted observations of liver function and fecal urobilinogen excretion. Thymol turbidity, thymic flocculation, and serum bilirubin, direct and total, were normal throughout the period of study in both subjects as was the bromsulfalein test in subject MNL 2. In subject MNL 1, the 45 minute bromsulfalein retention rose about 10 per cent eight days after infusion and persisted at about this level for 50 days, following which it returned to normal. In this subject the bromsulfalein retention had been, on one occasion, just before infusion, 7 per cent. Neither subject developed signs or symptoms of homologous serum jaundice.

RED CELL MASSES, PLASMA VOLUME, AND ERYTHROCYTE SURVIVAL IN A NORMAL MALE MADE POLYCYTHEMIC BY ERYTHROCYTE INFUSIONS

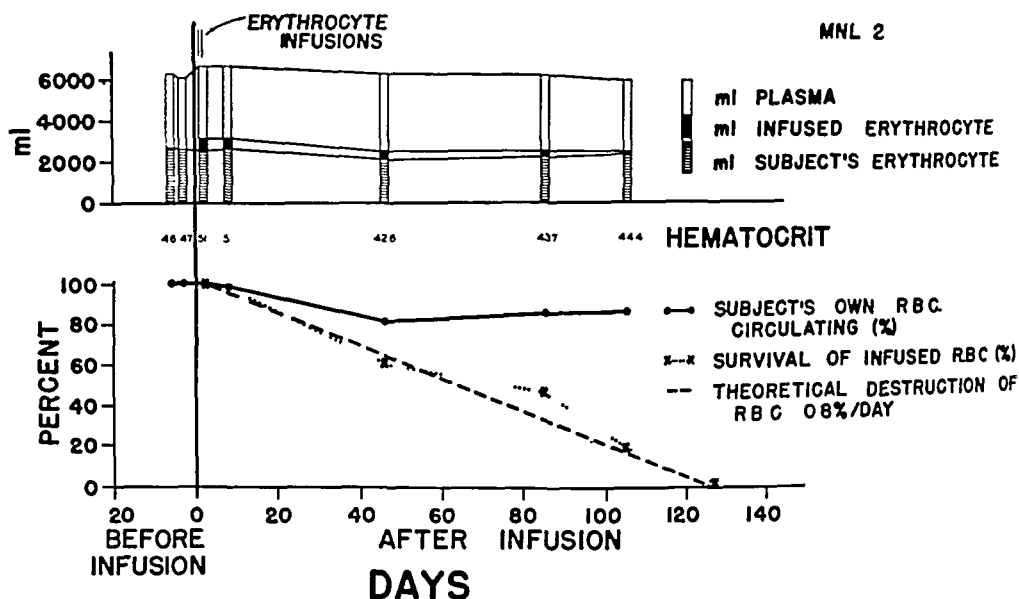


FIG 4—Plasma volumes, hematocrits, and red cell masses in a normal male made polycythemic by erythrocyte infusions. The survival of the infused red cells is normal. There is an initial fall in the subject's own red cell mass during the first 48 days following infusion. Thereafter, the recipient cell mass increases progressively to about its preinjection level.

D Source of the Extra-Urinary Nitrogen Appearing After the Erythrocyte Infusions As indicated earlier, following the infusions of erythrocytes, there was a slow, steady excretion of "extra" urinary nitrogen of 0.5 to 1.0 Gm. per day over the preinjection mean values, which continued for about one month. During this time nitrogen mathematically equivalent to about 80 per cent of the infused red cell nitrogen was excreted. The infused red cells, however, were not the direct source of the "extra" nitrogen. In Figs 8 and 9 the "extra" nitrogen is plotted cumulatively, and the quantities of nitrogen equivalent

alent to the destroyed infused cells and the reduction in the recipient's own cell mass are also charted

As pointed out earlier, the observations of cell survival are consistent with normal survival of the infused red cells. As expected, the nitrogen equivalent of the observed decrease in the infused red cell mass agrees strikingly well with the calculated theoretical equivalent, assuming destruction of the infused

TABLE VII—*Liver Function and Fecal Urobilinogen Excretion in Normal Males Made Polycythemic by Erythrocyte Infusions*

Day of Study	Total Erythrocyte Mass (ml)	1 st Serum Bilirubin (mg/100 ml serum)	Total Serum Bilirubin (mg/100 ml serum)	Bromsulphalein (% retention at 45')	Thymol Turbidity (units)	Thymol Flocculation (units)	Period of Study (days)	Fecal Urobilinogen (mg/day)
Subject MNL 1								
<i>Before Infusion</i>								
24		0.05	1.0	3	2	0	16 thru 12	125
17	1800							
10		0.05	1.9	7	3	0	11 thru 7	210
6	1820						6 thru 1	180
<i>After Infusion</i>								
8		0.05	0.6	11	3	0	1 thru 4	170
16	2535	0.07	1.0		3	0	5 thru 9	170
22	2175	0.19	1.9	9	4	0	10 thru 14	190
51	1800	0.12	1.9	10	2	0		
87	1850	0.20	1.6	2	2	0	15 thru 19	185-
108		0.12	1.6	1	1	0	20 thru 23	195
							24 thru 28	165
							29 thru 33	190
							34 thru 38	175-
Subject MNL 2								
<i>Before Infusion</i>								
24		0.02	1.4	1	2	0	16 thru 12	155
10		0.19	1.5	3	2	0	11 thru 7	155
6	2695						6 thru 1	120
3	2600							
<i>After Infusion</i>								
8	3182	0.10	0.8	6	3	0	1 thru 4	175
16		0.20	2.6		3	0	5 thru 9	140
22		0.30	2.1	3	4	0	10 thru 14	215
48	2465	0.12	1.3		2	0	15 thru 19	200
86	2450	0.10	1.1	2	2	0	20 thru 23	115
107	2380	0.12	1.7	1	2	0		

cells at a normal rate of 0.8 per cent per day. The nitrogen equivalent of the destroyed infused cells thus accounts mathematically for about one-third of the "extra" nitrogen excreted. The remainder was accounted for mathematically, in the most part, by the nitrogen equivalent of the observed decrease in the subject's own red cell mass.

DISCUSSION

Among the many devices which have been employed profitably in elucidating problems of nitrogen metabolism, the use of the balance study has proved to be of great value. By comparing the total output of a given substance with the intake during a given period, although no specific information of intermediary metabolism is gained, an estimate may be had as to the overall metabolic processing of the material under study. The validity of such balance data is predicated on the ability of the investigator to determine with exactitude the metabolically active amounts of the substance under study which have been introduced into and excreted by the organism during a given period. Such determinations include not only accurate chemical analyses of the raw

BONE MARROW DEPRESSION FOLLOWING ERYTHROCYTE INFUSIONS

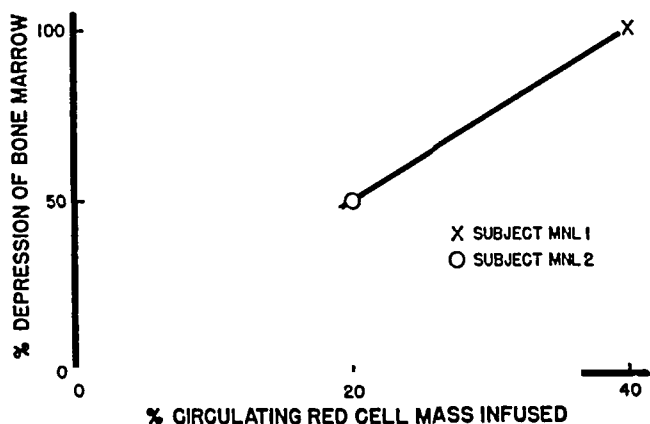


FIG 5—Apparent bone marrow depression in normal males made polycythemic by erythrocyte infusions. The apparent bone marrow depression following the erythrocyte infusions was directly proportional to the relative quantity of red cells infused.

materials participating in the balance, but also knowledge of the rapidity with which the nutrient substances actually take part in the dynamics of the metabolic pool. If a material which has been ingested by, or injected into, an animal is not metabolically active during the time of study, it is evident that balances constructed on mere total intake and output data for this period represent mathematical artefacts rather than accurate indices of the actual processing of the nutrient substance.

In the study of protein metabolism, reasonably accurate methods have long been available for the determination of nitrogen content in foodstuffs and excretory products of the organism. The limits of accuracy of such determinations are fairly well known and the significance of data obtained may be scrutinized in light of the probable errors involved. However, in respect to the metabolic fate of a nutrient following its introduction into the organism, knowledge is less complete. It appears that ingested dietary protein, peptides

LIVER FUNCTION
AND
FECAL UROBILINOGEN

IN A NORMAL MALE MADE POLYCYTHEMIC
BY ERYTHROCYTE INFUSIONS

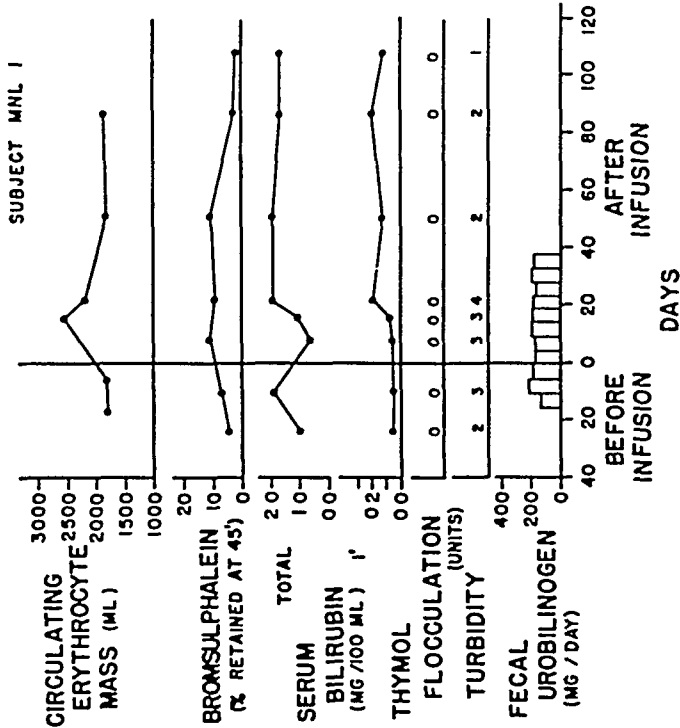


Fig 6—Following the infusions, thymol turbidity, thymol flocculation, and serum bilirubin remained normal. The 45-minute bromsulphalein retention was increased slightly during the period eight to 50 days post-infusion. Fecal urobilinogen excretion was not markedly increased following the erythrocyte infusions. This is in keeping with destruction of the increased total red cell mass at a normal, not an increased, rate.

LIVER FUNCTION
AND
FECAL UROBILINOGEN

IN A NORMAL MALE MADE POLYCYTHEMIC
BY ERYTHROCYTE INFUSIONS

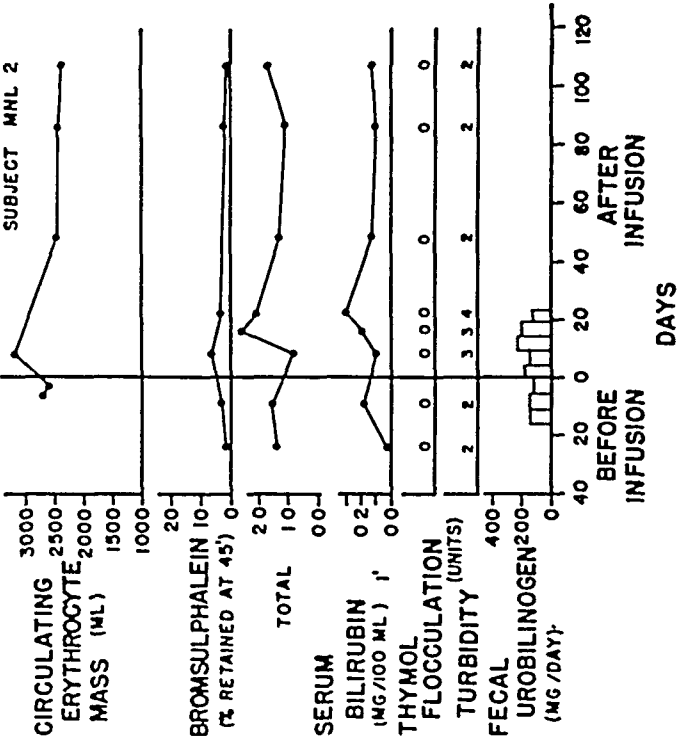


Fig 7—Following the infusions, thymol turbidity, thymol flocculation, serum bilirubin, and bromsulphalein clearance remained normal. Fecal urobilinogen increased slightly, quantitatively in keeping with destruction of the increased total red cell mass at a normal, not an increased, rate.

and amino acids are processed rather rapidly. This is suggested by measurement of amino acid levels in the blood following a protein meal¹⁷ and through consideration of the specific dynamic action of ingested protein upon the basal metabolic rate¹⁸. Such work indicates that the metabolism of the animal begins to feel the impact of ingested protein in a matter of hours, and that its overall rate may be assayed with reasonable accuracy in terms of a few days. The work of Schoenheimer and Rittenberg¹⁹ has conclusively demonstrated that nitrogen ingested as amino acids in the rat is widely disseminated throughout the body within three days following ingestion. It is probable that had their studies been conducted on the basis of shorter time intervals, a still more rapid diffusion of dietary nitrogen would have been demonstrated.

NITROGEN METABOLISM AFTER INFUSION OF ERYTHROCYTES

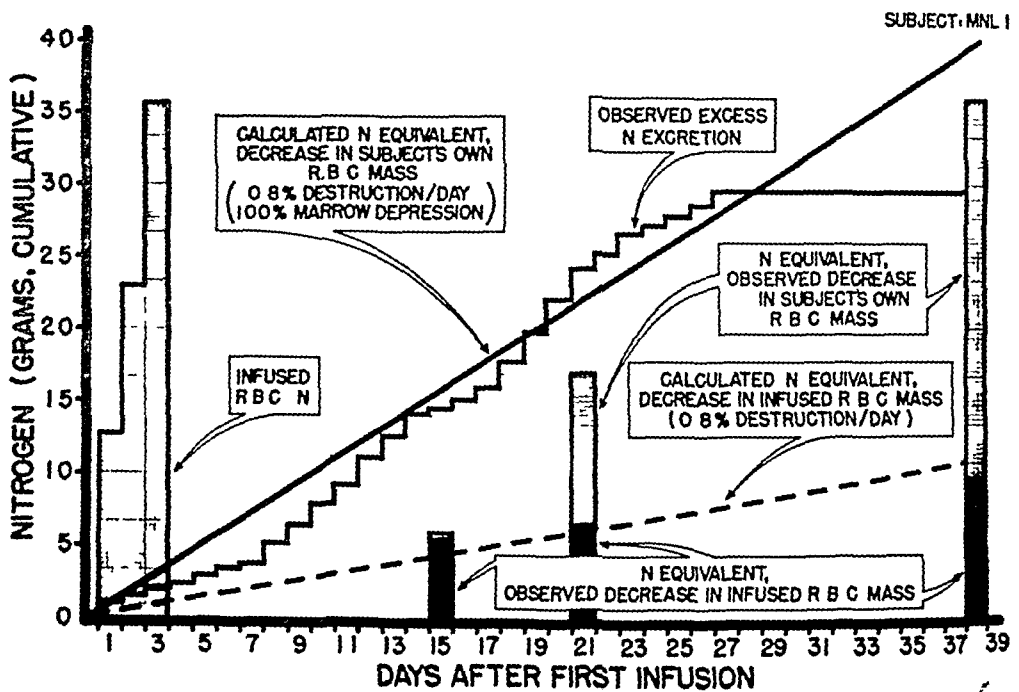


FIG 8—(Subject MNL 1) The nitrogen equivalent of the destroyed infused cells accounts mathematically for about one-third of the "extra" nitrogen excreted following erythrocyte infusions in a normal male. The remainder can be mathematically accounted for, in the most part, by nitrogen apparently diverted from normal erythropoiesis.

In recent years, both clinicians and research workers have been assisted by the availability of many nitrogen preparations capable of parenteral administration. Of chief interest among such preparations are four classes of substances: amino acid mixtures, protein hydrolysates (peptides and amino acids), plasma proteins, and whole blood. In regard to the first two classes, it would appear that intravenously injected amino acids and some short chain polypeptides are quickly deaminized or converted into body protein. Injection of such materials finds almost immediate reflection in increased urinary nitrogen excretion in calorically deficient subjects. The greater part of excreted

nitrogen takes the form of end products of protein metabolism (urea and ammonia) rather than of unchanged amino nitrogen. This holds true, in general, only when the natural isomers of the amino acids are used. Unnatural isomers of some amino acids, and certain peptides of some protein hydrolysate preparations are, for the most part, excreted unchanged.

Concerning the use of plasma protein as a source of parenteral nitrogen, it has been demonstrated by Whipple and his colleagues²⁰ that injection of such material into dogs as the sole source of nitrogen will promote true balance, and, of more importance, will maintain animals in good health over long

NITROGEN METABOLISM AFTER INFUSION OF ERYTHROCYTES

SUBJECT MNL 2

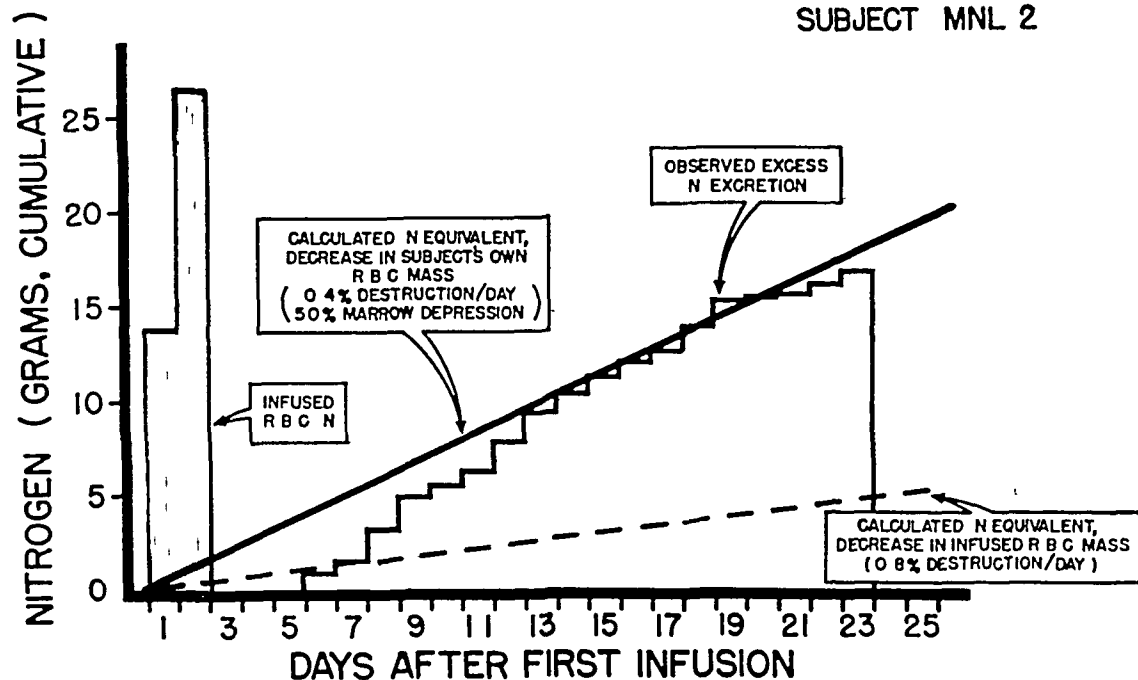


FIG 9—(Subject MNL 2) The nitrogen equivalent of the destroyed infused cells accounts mathematically for about one-third of the "extra" nitrogen excreted following erythrocyte infusions in a normal male. The remainder can be mathematically accounted for, in the most part, by nitrogen apparently diverted from normal erythropoiesis.

periods of time. Whipple has also demonstrated,²¹ through the introduction of N-15 labeled plasma proteins, that diffusion of the injected protein from the circulation occurs rapidly. Similar results were also obtained by Seligman and Fine²² using plasma labeled with radioactive sulfur and with bromine. A note of caution in the acceptance of such data as indicating prompt entrance of the injected plasma protein in the metabolic pool, is provided by the work of Albright,²³ Eckhardt²⁴ and others,²⁵ who have demonstrated in both normal and hypoproteinemic patients that utilization of injected plasma protein is delayed, ordinarily not beginning until a few days after infusion. Thereafter, the plasma protein is utilized slowly over a period of one or more weeks.

By the use of balance studies, Albright²³ noted that while disappearance of the injected plasma protein from the circulating blood may have been rapid, nitrogen, potassium, sulfur and mineral balances failed to reveal complete "burning" of the plasma or its deposition as body protein until the end of the indicated period. Even if part of the infused material had been immediately incorporated into body protein unchanged, as suggested by Whipple, it appears improbable that such new tissue formation would not have been reflected by changes in the balance of potassium, calcium, phosphorus and sulphur. Similar slow metabolic turnover has also been shown for injected serum albumin.²⁶ Such a finding as this may in part explain why some investigators have found it relatively easy to achieve *mathematically positive* nitrogen balance with plasma protein or albumin given intravenously. However, it is clear that the immediate metabolic implications of such apparent positive balance are quite different from those of a positive balance attained with oral protein. While such intravenously administered protein may serve as immediate replacement for plasma protein and a source of nitrogen for the organism over a long period, conclusions in regard to its immediate nutritional efficacy reached on the basis of short term studies must be guarded.

Confusion similar to that outlined above has existed in the consideration of erythrocytes as a source of parenteral nutrition. Seriously ill surgical patients commonly receive many blood transfusions, and it is important to know to what extent the erythrocytes of transfusions contribute to the daily nutritional requirements of these patients.

It is established that the life of normal fresh infused erythrocytes injected in tracer amounts to the normal subject varies between 120 to 130 days. Further, it is improbable on the basis of present evidence that the protein of the erythrocyte takes an active part in the protein metabolic pool of the body as long as the red cell is intact. Whipple²⁰ has concluded from his observations that hemoglobin in its production may draw on the plasma protein but that hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool. Moreover, the work of Shemin and Rittenberg²⁷ with red cells tagged by the administration of N-15 glycine has indicated that, unlike other body nitrogenous compounds, the heme of the red cell retains its labeled nitrogen unchanged throughout its life time. Grinstein, Kamen and Moore,²⁸ using glycine labeled with C¹⁴ in the carboxyl position, have shown that the globin moiety of hemoglobin also remains within the red cell during its life span without participating in the dynamic protein interchange characteristic of nucleated cells.

If metabolic effects are to be seen, then, from the infusion of erythrocytes as a source of protein, it would appear likely that these effects must come about either as a result of destruction of the red cell with liberation of its protein for use by the body or from secondary effects of red cell infusions, such as the production of concomitant marrow depression with liberation of the protein ordinarily utilized for erythropoiesis.

In regard to the questions of bone marrow depression and increased erythrocyte destruction, there is evidence indicating that in certain pathologic conditions survival time of the red cell may be materially shortened. Moore and Cope,²⁹ studying post-burn anemia, were able to demonstrate with the use of radio-iron an apparently increased rate of blood destruction in burned patients. This occurred over and above that noted as a result of the initial hemolysis of erythrocytes produced, probably by the heat, at the time of burning. In addition, these workers felt that some marrow depression occurred in the post-burn state. In regard to other pathologic conditions, Ashby³⁰ has brought forth evidence that the longevity of the red cell may, on occasion, be materially shortened.

When an actual plethora of red cells exists as opposed to anemic conditions described above, some authors have postulated an increased rate of cell destruction. Earlier experimental work in animals was alleged to have demonstrated this phenomenon.^{31, 32} For the most part, rabbits and dogs were used. This early work is open to the criticism that development of isoimmune factors were not given sufficient consideration in evaluation of the data. It is probable that such factors may have played a part in the allegedly increased destruction.

Krumbhaar³³ found that despite the intravenous introduction into dogs of large quantities of nitrogen in the form of whole blood, the total nitrogen, urea, and ammonia in the urine and feces was not appreciably raised for some time after the onset of the plethora. He states that Forster^{34, 35} and Tschirnew³⁶ also had failed to observe an appreciable rise in nitrogen output following homologous blood transfusions in dogs. Miller *et al*³⁷ have reported studies on one protein-deficient, anemic dog given large amounts of washed red cells intraperitoneally. A total of 163 Gm of hemoglobin was given and a net production of 173 Gm hemoglobin and 56 Gm plasma protein was recorded. This study is difficult to interpret, since it was not possible to differentiate between red cells produced and red cells absorbed intact from the peritoneal cavity. Further, the amount of red cell destruction, which may be fairly considerable when large quantities of washed erythrocytes are given intraperitoneally, was not quantitated.

Kremen² in his review outlines the belief of Melnick³⁸ and associates that "the slow continuous breakdown of injected red blood cells after plasmaphoresis experiments liberated globin which is completely metabolized similar to dietary protein."

In a brief abstract, Taylor and Lytle³⁹ have expressed the belief that protein of the erythrocyte "is not available for conversion into plasma proteins" over short periods of time. Lacking information as to further experimental details of this study, no statement can be made as to the validity of this conclusion.

Kremen² in a short term study of malnourished patients with malignancies infused whole blood intravenously as the sole source of nitrogen intake in amounts sufficient to produce a transient polycythemia. Although apparent

positive nitrogen balance was attained, the red cell protein was apparently not immediately available for general body needs as judged by the failure of extra nitrogen to appear in the urine and the apparent persistence of the infused cells. Pace and his co-workers⁴⁰ noted a return of the hematocrit to normal in about 50 days in normal subjects made polycythemic by transfusions. The possibilities of increased cell destruction and/or depressed bone marrow function were discussed, the authors inclining to the latter as more likely. No quantitative assay of bone marrow activity or changes in red cell mass were obtained.

In the present study nitrogen balance and erythrocyte survival in subjects made significantly polycythemic by the infusion of fresh, separated, serologically identifiable red blood cells were followed. Normal adult males at, or near, nitrogen equilibrium were used as test subjects in order to reduce variables to a minimum and to make interpretation relatively straight-forward. When such individuals are on a fixed diet, and the intake of metabolically active nitrogen is suddenly increased, most of the additional intake nitrogen is excreted in a relatively short time, since the body appears to have little capacity for storage of surplus nitrogen under these conditions. By noting the urinary nitrogen excretion following the infusion of erythrocytes, and, in addition, quantitating the survival of erythrocytes, both donor and recipient, it should be possible to estimate the availability of transfused red cell nitrogen to the general body metabolic pool.

Beginning shortly after the infusions in both subjects, extra-nitrogen, 0.5 to 1.0 Gm daily over and above the preinjection control mean values, appeared in the urine, while fecal nitrogen was unchanged. The increased urinary nitrogen excretion persisted for about one month, following which nitrogen equilibrium was again attained. Although the subjects received different quantities of red cells, and excreted different absolute amounts of excess nitrogen, the excretion was proportionately the same. By the time nitrogen equilibrium was reattained extra nitrogen mathematically equivalent to about 80 per cent of the infused red cell nitrogen had been excreted. The infused red cells, however, were *not directly* the source of the extra-urinary nitrogen. Following the infusions, the initially increased red cell masses and hematocrits fell progressively, and returned to the preinjection level in about 40 days. Pace and his co-workers³⁸ observed a return to normal of the hematocrit in their transfused subjects in a similar length of time, and concluded that there may have been an increased destruction of infused cells. However, this is not the case. Although the hematocrits and red cell masses returned to the preinjection level, this was not due to an increased destruction of the infused cells. On the contrary, the survival of the infused cells was normal.

On the other hand, the levels of the subjects' own cells were not maintained at first, but fell progressively. This fall appears to have been due to concomitant marrow depression, since it is unlikely that the subject's own cells would have been destroyed at a rate faster than that of the infused cells.

Further, the observed fecal urobilinogen excretions were at levels consistent with normal destruction of the total red cell mass, not increased destruction. The decrease in erythropoiesis was related to the quantity of red cells infused. Thus, the first subject received infusions amounting to 40 per cent of his original red cell mass and demonstrated essentially complete marrow depression, while the second received infusions amounting to 20 per cent of his original red cell mass, and demonstrated about 50 per cent marrow depression. Preliminary examination of sternal bone marrow smears corroborates the apparently diminished erythropoiesis. White cell production was not impaired. The apparent depression of erythrocyte production was only temporary, since as soon as the total circulating red cell mass returned to the preinjection level erythrocyte regeneration proceeded at about a normal rate. More prolonged marrow depression than was observed in this study has been reported following multiple transfusions in a patient with transient thrombocytopenic purpura.⁴¹ The pathogenesis of marrow depression under the conditions of artificially induced polycythemia outlined in the present study is not clear. It has been suggested⁴² that erythropoietic activity may be related inversely to the blood oxygen content.

As earlier indicated, extra nitrogen, mathematically equivalent to about 80 per cent of infused red cell nitrogen, was excreted in a period of a month following the infusions. Quantitatively, however, the nitrogen equivalent of the destroyed infused cells accounted for only about one-third of the extra nitrogen excreted. The remainder could be accounted for, in the most part, by the nitrogen equivalent of the observed decrease in the subject's own red cell mass. It would appear, then, that the observed excess urinary nitrogen following erythrocyte infusions in normal males on a fixed, adequate diet derives in part from the infused red cells, and in part from nitrogen diverted from normal erythropoiesis. It is not implied that the nitrogen appearing in the urine is specifically that of the infused red cells, or that which has been diverted from red cell synthesis, but rather that quantitatively equivalent amounts are involved. The well-known interrelationships of the body nitrogen metabolic pool would negate strict identity.

It is not possible to state with assurance the effect on nitrogen metabolism of the brief influenza-like illness which occurred shortly after the infusions. It is our impression that considering the mildness of the attacks, the effect was minimal and does not introduce any serious difficulties into the interpretation of the study.

It should be pointed out that the quantity of nitrogen which might be available as a result of depressed erythropoiesis even if complete, is small, amounting to only about one Gm per day. Only a similar relatively small quantity can be expected from the normal breakdown of infused cells. Further, the biologic efficiency of liberated globin as a protein food-stuff in man is not established.^{43, 45}

It is clear that nitrogen made available to the metabolic pool as a result of erythrocyte infusions is not great, is made available only over a period of weeks, is of unknown biologic efficiency, and quantitatively would contribute little to the overall nutritional requirements. Whether this process is accelerated in patients during catabolic or anabolic conditions is to be studied.

CONCLUSIONS AND SUMMARY

The metabolic fate of infused erythrocytes in adults made significantly polycythemic by transfusions has not been known. Only inadequate and incomplete information has been available on erythrocyte survival and bone marrow function in such individuals. Data on these points were obtained in two normal adult males on a constant diet receiving serologically identifiable, fresh, separated erythrocytes. Observations were made on body weight, nitrogen balance, circulating plasma protein and erythrocyte mass, erythrocyte survival, serum bilirubin concentration, urobilinogen excretion, and liver function.

Plasma volumes, liver function, and circulating plasma proteins were essentially unchanged throughout the period of the study. Survival time of the infused erythrocytes was not shortened. The infused red cell mass decreased at a normal, expected rate of 0.8 per cent per day. Concomitantly, the mass of the recipient's own erythrocytes declined at a rate of 0.4 to 0.8 per cent per day in direct proportion to the relative amount of the infusions. This progressive fall in the subject's own erythrocyte mass was probably due to erythropoietic depression rather than to abnormally increased destruction. This is suggested by the normal survival of the infused erythrocytes and by urobilinogen excretion consistent with breakdown of the total red cell mass at a normal, not an increased, rate. There was a direct linear relationship between the extent of apparent bone marrow depression and the degree of induced polycythemia.

A slow, steady excretion of 0.5 to 1.0 Gm of nitrogen per day (above the control equilibrium value) began shortly after the infusions and continued for one month. The total extra nitrogen excreted was mathematically equivalent to 80 per cent of nitrogen content of the infused erythrocytes. However, this excess nitrogen derived only in small part from the infused red cells. The greater part could be accounted for almost completely by nitrogen diverted from normal erythrocyte synthesis as a result of apparent marrow depression.

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DISCUSSION —DR CHARLES C LUND, Boston, Mass Dr Levenson and his associates should be congratulated on this careful and rather complicated piece of work When Dr Levenson was working with Taylor and me and others of my associates during the studies of burns during the war, Taylor and I had many battles as to what to do with charting the nitrogen that went into these patients in the form of whole blood However, what you do about getting up your records is not as important as what happens to the patients and what this means to the patients

The members of this Society, with a long series of studies presented by Elman and Ravdin and others on nitrogen metabolism and studies concerned with transfusion, have a pretty clear idea that blood and nutrition both are needed in the long-time very sick patient As I talk with people and see patients, a little away from the top medical centers, there still are a great many doctors who know that patients need to be fed, but they don't know the quantitative implications of feeding when continuing losses are taking place, and they are satisfied that they are doing enough to feed the patient if they give a unit or two of plasma, or give some blood It is surprising how frequently you run into patients who could easily be given either oral or other feeding by those doctors who are perfectly happy that they are taking care of the patients with blood

This paper is one more to show that the treatment for lack of blood and the treatment for lack of food must be clearly differentiated, and you cannot use one for the other

DR F ROSS BIRKILL, Chicago, Ill I wish to thank Dr Lund for his helpful comment and criticism of this work In summary, it should be emphasized that the nitrogen available from erythrocyte infusions may be considered to come from two sources—either from destruction of the red cells themselves or from concomitant marrow depression We have shown in this study that significant marrow depression indeed does occur, as evidenced by a fall in the erythrocyte mass of the recipient

We found, as a result of marrow biopsies, that the myeloid-erythroid ratio was materially changed as a result of these infections, and definite marrow depression resulted A certain amount of nitrogen is to be expected from such depression, and many glowing reports have appeared in the literature postulating a flood of nitrogen from such marrow depression, but it is evident that the erythropoietic centers, which have been accustomed to maintaining a normal red cell volume, can release about 1 Gm or at the most $1\frac{1}{2}$ Gm of nitrogen daily

As a result of this, it is perfectly evident that the amount of nitrogen available from some such erythrocyte depression is inconsequential in providing for the nutritional needs of the patient or in reversing the catabolic phase

The other source of possible nitrogen, of course, lies in the destruction of the red cells themselves, and we have shown here that such destruction is roughly normal in normal subjects made polycythemic That increased destruction may on occasion occur in other patients, debilitated, and the like, cannot be denied Winifred Ashby has put forth evidence to indicate that in various pathological states increased destruction of infused red cells may occur It has been brought forth many times also that in the post-burn phase, long after the acute thermal trauma to red cells, there occurs a continuing destruction of red cells, at times up to 200 cc of red cells per day

However, it is very doubtful that such a condition obtains in the variety of conditions with which the surgeon is faced in his nutritional requirements Therefore, it may be said that the red cell infusions really mean relatively little to the patient from the standpoint of released nitrogen

As Dr Lund has emphasized, it is of no consequence to him that a mathematically positive balance has been maintained by the surgeon The important factor is whether or not the infused protein is immediately available for his nutritional needs and for the reversal of the catabolic phase, which, as can be seen from previous discussion, probably cannot be varied as an entity as yet

Therefore, with this evidence we must view with some caution studies in the literature which have reported to reverse catabolic phases, which have purported to maintain patients in good nutritional balance when red cells have been used as a significant part of their daily nitrogen requirements. Before we can evaluate properly such studies, we must know the extent of marrow depression, if any, which has been consequent upon such infusions.

In all probability the nitrogen released is insignificant. We must know the amount of red cell destruction. It appears likely that in the majority of conditions the nitrogen thereby released is also insignificant for nutritional needs, and, lastly, we must know more of the biological value of the red cell protein, namely, globin, for it has been shown to be an incomplete protein lacking certain of the essential amino acids.

Until such information is forthcoming we must hesitate to evaluate finally such studies.

AN EVALUATION OF OXYGEN THERAPY*

PHILIP B PRICE, M D , RALPH C RICHARDS, M D , AND
JAMES B HAMMOND, M D

SALT LAKE CITY, UTAH

OXYGEN IS USED extensively as a therapeutic agent, but not always with discrimination

The usefulness of oxygen administration has long been a subject of investigation and discussion. Although its theoretical limitations are set forth in textbooks of physiology, and Goodman and Gilman¹ state clearly that "with few exceptions, the therapeutic usefulness of oxygen is in anoxic anoxia," yet in practice, oxygen is customarily administered for all sorts of conditions—to almost any patient, indeed, whose vital functions are threatened. In an influential article, Boothby, Mayo and Lovelace² assert that administration of 100 per cent oxygen combats shock, and they recommend the employment of oxygen immediately after operation in all patients who have undergone extensive surgical procedures. Judd³ is quoted as saying "There can be no question that the use of oxygen is a valuable aid in the immediate postoperative care of patients for which surgical treatment has been carried out on account of some serious abdominal conditions." The new generation of physician-anesthesiologists are enthusiastic and generous users of oxygen. On the other hand, Blalock⁴ expresses the clinical experience of many surgeons when he says, "Inhalation of oxygen in the treatment of traumatic shock has been disappointing."

On theoretical grounds it has been urged that administration of high concentrations of oxygen raises the oxygen content of hemoglobin slightly, and the oxygen content of plasma even more, that is to say, when the patient breathes pure oxygen, his blood may contain up to one-seventh more oxygen than when he breathes air. That would appear to be a worthwhile gain for any patient threatened with anoxia.

The answer to that line of reasoning is that oxygenation is a very complex physiologic and physico-chemical process. Oxygen tension in the blood leaving the lungs is only one of many interrelated variables. There are also matters of adequate respiration, integrity and efficiency of the circulation, ability of blood to give up oxygen to the tissues, and ability of the tissues to utilize delivered oxygen. None of these aspects taken alone can be considered a reliable indication of the degree of oxygenation as a whole. A slight increase in oxygen content of arterial blood, for example, might be more than counterbalanced by a concomitant slowing of the blood flow.

The only single test that provides an accurate measure of oxygenation as a whole is the minute volume of oxygen uptake. Since the body cannot store oxygen, the quantity of gas absorbed by the lungs in a period of time represents the exact quantity used by the body during that time. Oxygen consumption is the algebraic sum of all the variables influencing oxygen utilization.

* Read before the American Surgical Association, April 22, 1949, St. Louis, Missouri

If the beneficial effects of oxygen therapy are due to an increase in total oxygen consumption, then there should be a measurable difference between oxygen consumed by an individual breathing air as compared to the same individual breathing pure oxygen. It was with this idea in mind that the following study was begun.

TABLE I—*Peripheral Circulatory Failure*

Produced by	Effects of Oxygen
Hemorrhage	No appreciable clinical improvement
Extensive burn	
Intestinal obstruction	No significant increase in oxygen uptake
General peritonitis	
Crush of extremities	
Histamine injection	

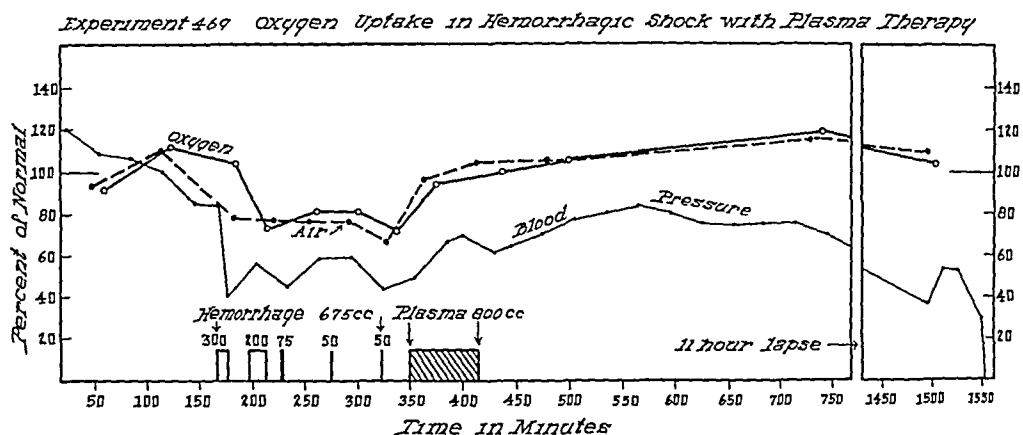


FIG 1—A representative experiment in which severe hemorrhagic shock was treated with plasma with temporary improvement but fatal outcome, as indicated by the blood pressure curve. The heavy solid line (labeled "oxygen") indicates the oxygen uptake when the dog was breathing pure oxygen, the broken line (labeled "air") represents oxygen uptake when breathing atmospheric air. It is obvious that throughout the experiment, during the basal period and also during early and late shock, oxygen consumption was similar when breathing air and breathing oxygen.

EXPERIMENTS

Oxygen uptake was measured in about 75 narcotized dogs which were made to breathe first atmospheric air and then approximately 100 per cent oxygen. The gases were administered alternately in accurately measured amounts through a closed system, in which was incorporated a pair of calibrated, water-sealed, BMR spirometers connected to the animal by a cuffed endotracheal tube.

Experiments were in three groups. First, shock was produced in several different ways (Table I). In none of these experiments, during either early or late shock, was administration of oxygen followed by any apparent clinical improvement, or any significant increase in oxygen uptake.

Figure 1 illustrates a typical experiment. This dog was bled severely. When his condition became critical, he was given plasma which prolonged his

life although he died eventually from peripheral circulatory failure. Throughout the experiment, breathing oxygen and breathing air were equally efficacious.

Figure 2 shows a similar result in an animal which, after bilateral lumbar sympathectomy, was subjected to compression of both thighs. A typical acute crush syndrome ensued which was rapidly fatal. Again, it will be noted that breathing air and oxygen had equal effects upon oxygen uptake.

In our second set of experiments (Table II), central circulatory failure was produced by cardiac tamponade. Pressure of fluid in the pericardium was

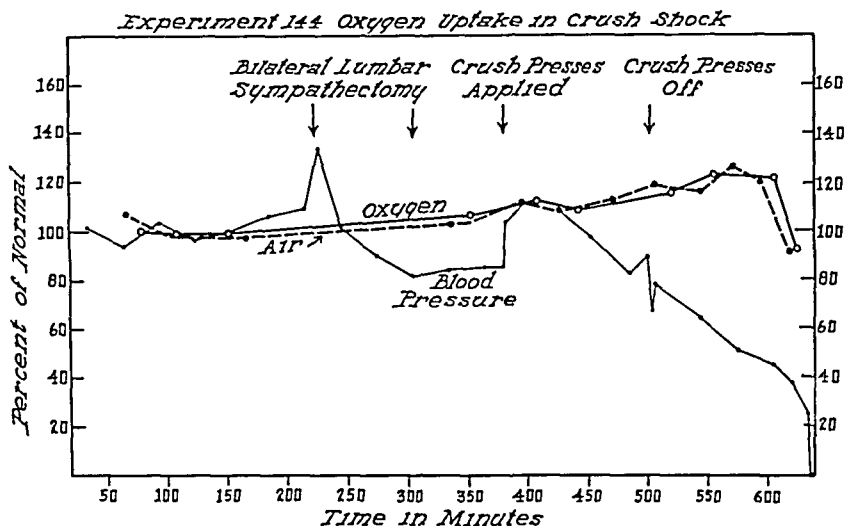


FIG 2—A representative experiment in which, following lumbar sympathectomy, crushing force was applied to the dog's thighs for 2½ hours. Rapidly fatal shock ensued. Throughout this experiment air-breathing and oxygen-breathing had equal effects, as far as oxygen consumption was concerned.

TABLE II—Central Circulatory Failure

Produced by	Effects of Oxygen
Cardiac tamponade	<div> No appreciable clinical improvement </div> <div> No significant increase in oxygen uptake </div>

increased by increments until the animals finally died. In this condition also, administration of oxygen did not improve the animals clinically, and did not increase oxygen consumption.

In a third group of experiments (Table III), respiration was embarrassed in various ways by tracheal obstruction, by prolonged inspiratory resistance, by pneumothorax and hydrothorax, by central respiratory depression with morphine and barbiturates, and by external pressure on the thorax and abdomen. In mild degrees of respiratory interference, without cyanosis, breathing pure oxygen was of no appreciable value. When respiratory embarrassment was enough to cause slight cyanosis, oxygen relieved the cyanosis, although oxygen consumption per minute was not increased. In severe degrees of respiratory dysfunction, however, oxygen improved the cyanosis and caused a significant increase in oxygen uptake.

Figure 3 illustrates a representative experiment in which we made the dog breathe against inspiratory resistance in an unsuccessful attempt to produce pulmonary edema. It is clear that in this condition oxygen consumption was increased by oxygen administration, although there was a manifest tendency toward compensation, so that after a time air-breathing became just as effective as oxygen-breathing. It will be noted also that sudden falls in blood pressure occurred whenever oxygen was given.

TABLE III—*Respiratory Dysfunction*

Produced by	Effects of Oxygen
Central respiratory depression	In mild respiratory embarrassment (with out cyanosis) no appreciable benefit
Tracheal obstruction	
Prolonged inspiratory resistance	In moderate respiratory embarrassment (with cyanosis) cyanosis relieved but no increase in oxygen uptake
Pneumothorax or hydrothorax	
Constriction of chest and abdomen	In severe respiratory embarrassment cyanosis reduced clinical improvement increased oxygen uptake

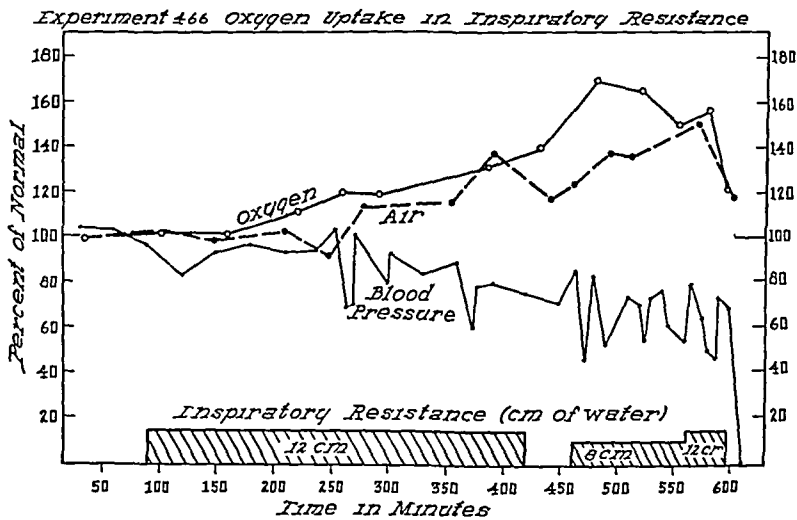


FIG 3—A representative experiment in which the dog was made to breathe against inspiratory resistance for many hours. The rising curve of oxygen consumption indicates increasing demands for oxygen that could not be met during the last 2½ hours, in consequence of which the animal died from anoxia. It is clear that breathing oxygen was of some benefit in this case.

Another example of respiratory embarrassment is shown in Figure 4. The aforementioned effects of oxygen are again clearly demonstrated. With a moderate-sized pneumothorax there was slight cyanosis which was relieved by oxygen, although oxygen uptake was not increased. When the pneumothorax was increased, however, so as to cause severe embarrassment of respiration, the benefit from breathing oxygen became obvious, both in clinical improvement and in increased oxygen consumption. But here again, compensa-

tion occurred so that in the end air nearly matched pure oxygen in efficacy. Note also how the arterial blood pressure fell precipitately 20 to 40 mm Hg whenever oxygen was given, but rose promptly to its original level whenever the animal was permitted to breathe air again. This last effect was due, we believe, to the fact that the dogs, when given oxygen, breathed much more slowly and easily, but in the process the pumping action of dyspnea on venous return to the heart was largely lost. These drops in blood pressure were associated with, and in fact were caused by, proportionate sudden reductions in cardiac output.

We have had a number of dogs in late stages of shock, with coincident hypotension and respiratory embarrassment, that died suddenly upon administration of pure oxygen. On at least two occasions I have seen the same thing happen in patients. It is possible that in such cases breathing oxygen caused sudden fatal reduction of cardiac output.

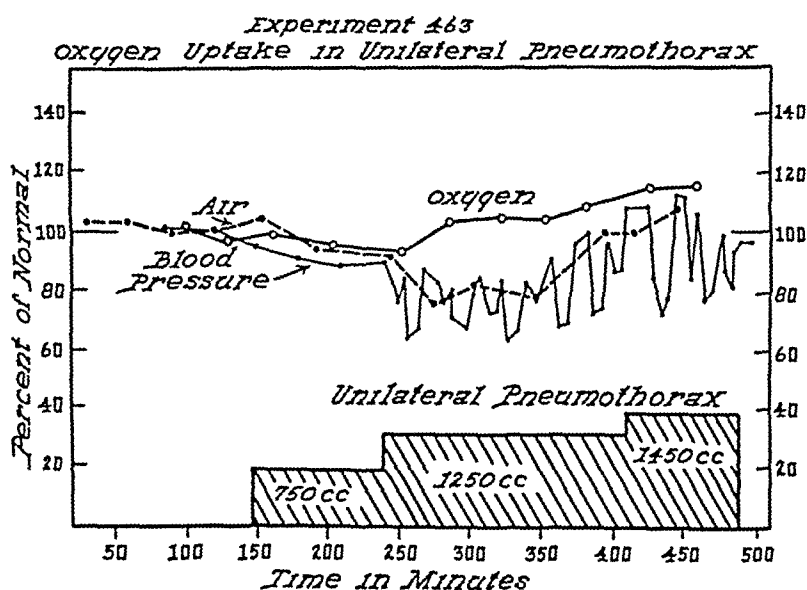


FIG 4—A representative experiment in which respiration was embarrassed by pneumothorax. The advantage of breathing oxygen under these conditions is manifest.

DISCUSSION

These experiments are believed to provide at least a partial answer to the questions, What are the indications for oxygen therapy? What does breathing oxygen actually accomplish?

In states of shock in which respiration remains unimpeded, administration of oxygen is of dubious value. Anoxia may indeed be present to a dangerous degree, but breathing oxygen will not correct it. In such cases, time and effort would be better spent in giving blood and blood substitutes, and in other measures designed to improve the failing circulation, for that is where the trouble lies. Restoration of an adequate circulation is the surest way—indeed, it is the only way—to correct the anoxia of shock.

Likewise, in cardiac tamponade, and presumably in other forms of cardiac failure also, if there is no associated pulmonary edema or other abnormality hindering respiration, administration of oxygen has limited value. Here again, the fault lies, not in failure of the blood to be fully loaded with oxygen as it passes through the lungs, but in deficient transportation of the oxygenated blood. In central circulatory failure, therefore, one's efforts should be directed principally toward improving the patient's depressed circulation and reducing, at least temporarily, his total oxygen requirements.

But if, for any reason, free and normal respiration is seriously intertered with, administration of oxygen is nearly always indicated. The greater the respiratory embarrassment, the more urgent the need of breathing oxygen. Even under these circumstances, however, oxygen administration is only palliative. The basic problem is to correct the respiratory dysfunction.

In "admixture cyanosis," in which a portion of the circulating blood passes, without being oxygenated through a non-functioning part of the lung, and returns to the left side of the heart to be mixed with oxygenated blood from the normal lung tissue, oxygen should be used, although the results are apt to be disappointing.

When circulatory failure and respiratory difficulty or disease coexist, oxygen should be given—with caution—perhaps combined with a judicious use to carbon dioxide. But here also it is a mistake to expect too much of oxygen. The best that can be hoped for is to tide the patient over a brief critical period while efforts are being made both to re-establish an adequate circulation and to relieve the respiratory embarrassment.

Although the term *anoxia* is used freely, even glibly, nowadays, actually it is often quite difficult to detect its presence or assess its degree. In extreme cases, such as in asphyxia or acute pulmonary edema, one glance at the deeply cyanotic terrified patient struggling for breath will suffice to establish a diagnosis of severe oxygen deficiency, but in other instances, a dangerous degree of anoxia may exist without any other manifestation than progressive deterioration of the patient's condition.

Symptoms of acute oxygen lack noted by aviators—lassitude, headache, altered respiration, fatigue, and psychic impairment—are not pathognomonic, for they commonly occur without anoxia. Dyspnea more often than not is simply a compensatory reflex act which successfully protects the body from anoxia. Cyanosis is not an infallible criterion. In polycythemia, it may be falsely present, in anemia and in carbon monoxide poisoning, it may be falsely absent, and in individuals with normal blood components, slight cyanosis may only indicate a high coefficient of oxygen utilization. Nor can measurements of arterial or venous oxygen content alone be relied upon to indicate the presence or degree of oxygen deficiency in the body as a whole. That is to say, anoxemia is not a true measure of anoxia.

The problem is complicated further by the uneven distribution of blood in the body, and by regional variations in blood flow. It is quite possible for one

part of the body to suffer oxygen lack while another part receives adequate amounts of oxygen. Blood oxygen measurements in the carotid, for example, or in the lobe of the ear, do not always tell us whether vital centers are or are not receiving all the oxygen they need.

In our present imperfect state of knowledge, the best that can be done, perhaps, is to recognize the problem, utilize all available clinical and laboratory tests, interpret them critically, and exercise diagnostic acumen and clinical judgment. If oxygen lack is suspected, but is thought to be due primarily to circulatory failure, reliance should not be placed on oxygen therapy. If, on the other hand, oxygen efficiency is thought to be present, and to be due primarily to respiratory dysfunction, oxygen should be administered. But in so doing, the weightier matters of correcting a failing circulation and relieving an embarrassed respiration must not be neglected. These we ought to do and not leave the other undone.

SUMMARY

It has been commonly assumed that when oxygen is administered to a patient his total oxygen consumption is increased. Doubts as to the validity of that assumption led to the present investigation.

The value of oxygen as a therapeutic agent was tested directly in animals by having them breathe air and oxygen alternately, and by measuring the amounts of oxygen consumed under comparable conditions.

In shock produced by hemorrhage, burns, intestinal obstruction, general peritonitis, crush of extremities, and histamine injections, administration of 100 per cent oxygen did not result in either clinical improvement or increased oxygen consumption.

Likewise, in central circulatory failure, produced by cardiac tamponade, it could not be demonstrated that breathing oxygen had any advantage over breathing atmospheric air.

However, when respiration was definitely embarrassed by central depression, tracheal obstruction, prolonged inspiratory resistance, pneumothorax, or constriction of the chest and abdomen, oxygen therapy was of demonstrable value. These animals showed clinical improvement, and the total oxygen uptake was increased.

Whenever pure oxygen was administered to dogs with respiratory difficulty, the relief of dyspnea was found to be associated with a fall in blood pressure of 20 to 40 mm Hg. This effect of oxygen may be dangerous if severe hypotension and dyspnea coexist.

These results should not be surprising. In hemorrhagic and traumatic shock the fault lies primarily in deficient blood volume and depressed circulation, not in failure of the blood to be aerated as it passes through the lungs, whereas, in anoxic anoxia the reverse is the case.

The clinical implications of these experimental observations are discussed

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DISCUSSION—DR JULIAN JOHNSON, Philadelphia, Pa Mr President, I am sure that Dr Price is correct in his implication that a great many patients receive oxygen therapy when it is not beneficial to them The inaccuracy of estimation of the arterial oxygen saturation based on the patient's color is well known An analysis of a sample of arterial blood requires trained personnel and is time consuming

Perhaps the simplest method of determining whether oxygen therapy is worthwhile is by means of the oximeter A base line blood analysis is not indispensable The oximeter can be placed on the patient's ear, and readings made when the patient is breathing air and oxygen No absolute value of arterial oxygen need be obtained However, if the relative arterial oxygen is not materially increased when the patient is given oxygen to breathe as opposed to air, it is unlikely that it is beneficial to him We have used this procedure for some time and have found that we use much less oxygen therapy than previously

SOURCES OF ERROR IN OXIMETRY*

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THE OXIMETER is a photo-electric device for continuous determination of the arterial oxygen saturation. As the method depends upon the differences in light absorption by the pigments oxyhemoglobin and reduced hemoglobin it is applicable to intact translucent tissue perfused by arterial blood. During the 14 years since the original work of Kramer¹ oximeter technics have been explored which promise valuable clinical adjuncts^{2, 3}. In addition to its usefulness for monitoring the surgical patient's condition the oximeter provides theoretically valid determinations of cardiac output,^{4, 6} oxygen consumption,⁷ residual lung volume,⁷ saturation time,^{8, 10} and various circulation time values^{9, 13}. These convenient rapid oximeter technics should attain wide clinical use with further improvement of the method. Considerable variability in the design of the various oximeters and in the results obtained by different workers necessitated an investigation of the factors influencing oximeter accuracy and reproducibility. This paper is a preliminary report of observations which will be described in further detail subsequently.

In principle the oximeter is a two-color photometer or colorimeter. As in spectrophotometry its operation depends upon the mathematical relationship between the absorption of light and the concentration of the absorbing substance. Ideally, this relationship is logarithmic as defined by Beer's law. In a multi-component system the absorption is additive. Since blood is essentially a two-pigment mixture for purposes of determining saturation, this relationship may be expressed mathematically as

$$\log \frac{I_o}{I_t} = (\epsilon_1 \text{HbO}_2 + \epsilon_2 \text{Hb}) d$$

I_o is the incident light, I_t the transmitted light, HbO_2 the amount of oxyhemoglobin, Hb the amount of reduced hemoglobin, and ϵ_1 and ϵ_2 their respective absorption coefficients whose values are constants at a given wavelength. The value d represents the length of the optical path and will also be a constant for this situation.

It is apparent that the amount of light absorbed will be a function of (1) the sum of the amounts of HbO_2 and Hb and (2) the percentage relationship

* Aided by a grant from the National Foundation for Infantile Paralysis. Read before the American Surgical Association, St Louis, Mo., April 22, 1949.

of these pigments. This implies that it will be impossible to differentiate between changes in the amount of total pigment and changes in the percentage composition merely by measuring light transmission at one wavelength or at one color.

If a measurement is taken at a second wavelength different absorption coefficients for oxyhemoglobin and reduced hemoglobin are obtained which may be used in a similar equation. If the ratio of these two equations is obtained, the result will be found to vary only between two limits representing 100 per cent oxyhemoglobin and 100 per cent reduced hemoglobin respectively, and it will be independent of the total amount of pigment present. Any mixture of oxyhemoglobin and reduced hemoglobin will have its appropriate intermediate value. Mathematically the equation is

$$\frac{\log \frac{I_{0\lambda 1}}{I_{t\lambda 1}}}{\log \frac{I_{0\lambda 2}}{I_{t\lambda 2}}} = \frac{(\epsilon_{1\lambda 1} \text{Hb} + \epsilon_{2\lambda 1} \text{Hb}) d}{(\epsilon_{1\lambda 2} \text{HbO}_2 + \epsilon_{2\lambda 2} \text{Hb}) d}$$

The numerators represent the measurements at wavelength (λ) 1 and the denominators the measurements at wavelength 2. The absorption coefficients have characteristic values at each wavelength.

Oxygen saturation is defined as the ratio of oxygen content to oxygen capacity. This can also be expressed as the ratio of oxyhemoglobin to total hemoglobin. One hundred per cent saturation is represented by all the pigment in the form of oxyhemoglobin, and 0 per cent saturation implies that all the pigment is in the form of reduced hemoglobin. Since this is essentially the information obtained by the light absorption measurements, the latter may be calibrated to read in percentage oxygen saturation.

The validity of the above assumptions depends upon the experimental confirmation of the expected logarithmic relationship. Kramer^{14, 15} and Drabkin and Austin^{16, 18} have confirmed the relationship for hemolyzed blood. Its application for oximetry involves light scatter of erythrocytes introducing marked deviations in transmitted light. Thus changes in total blood are not reflected as a linear function of the logarithm of transmitted light. Study of this factor shall be reported subsequently.

The optical density of blood is such in the visible region that only extremely thin cuvettes will transmit significant light. In the red and near infra-red, transmission is considerably higher, permitting the use of thicker cuvettes which are comparable in optical density to the arterialized ear. A region in the near infra-red is known at which the absorption coefficients of oxyhemoglobin and reduced hemoglobin are the same. If this region is used for the measurement at wavelength 2 the denominator of the equation is simplified. In this situation the total hemoglobin may be measured.

The above discussion has been based on established spectrophotometric principles which require that the light be monochromatic, the walls of the

cuvette parallel, the absorbing medium homogeneous, and that no other absorbing elements be present. In practice, oximetry has employed polychromatic light, non-parallel walls for the "cuvette," an unknown homogeneity of the medium, and tissue other than the blood absorbing considerable light. The influence of these deviations from the ideal require investigation for the development of quantitative oximetry.

Polychromatic colorimetry of existing oximeters does not afford a rigorous assay of the variable factors encountered in the transillumination of bloodless and perfused tissue. Complete spectral data pertaining to the oximeter have not been previously reported. Therefore spectrophotometry of the human ear has been undertaken to establish a preliminary working basis for the design of an improved oximeter.

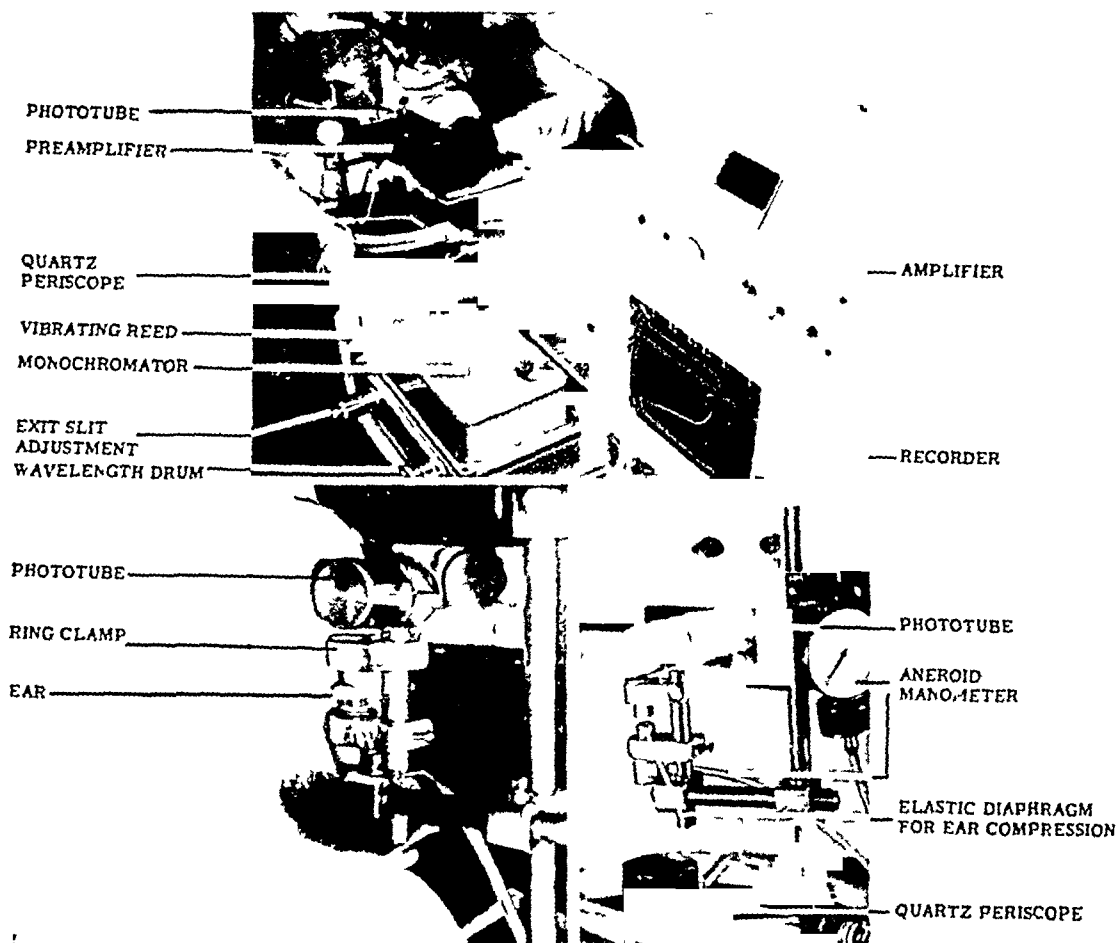


FIG. 1—Ear spectrophotometer

METHODS

The ear spectrophotometer. A Perkin-Elmer model 12 monochromator was modified to conduct the light from the exit slit via quartz prism to the ear of a recumbent subject (Fig. 1). A wavelength band of approximately 80 Angstroms in width was required to transmit sufficient light through the ear. An emission type phototube of the S-1 or S-4 spectral response was mounted above the ear to measure the transmitted light. The monochromatic beam was

interrupted at a frequency of 17 cycles per second by a vibrating reed to modulate the output of the phototube. The amplified AC signal was rectified and recorded by a continuous ink-writing potentiometer. The chart speed of the recorder was synchronized with the rotation of the Littrow prism of the monochromator so that the spectrum between 4,000 and 11,000 Angstroms was scanned and the transmission spectrum recorded automatically.* The ear of the subject was secured without compression in a ring clamp in which a transparent plexiglass cylinder covered by a translucent rubber diaphragm was applied to the surface of the ear (Fig 1). This cylinder was connected to a pneumatic pressure system to allow compression of the ear to an arbitrary pressure of 200 mm Hg. The spectral transmission of the bloodless and perfused ear were calculated as percentage transmission as follows

$$\% \text{ Transmission} = \frac{I_t}{I_o} \times 100$$

where I_t represents the recorded value of the transmitted light. I_o for the bloodless ear was taken as the phototube response at each wavelength without the ear in the optical path. I_o for the perfused or flushed ear was taken as the light transmitted at each wavelength by the bloodless ear.

The monochromator described above was also used to determine the spectral properties of various filters, photocells, and phototubes which have been employed in oximeters.

Experimental oximeters. Various earpieces were constructed, using selenium photocells as the light sensitive elements and various Wratten red and infra-red filters to obtain a two-color system. The breaker type amplifier described by Liston and associates,¹⁹ providing low input resistance, was used to amplify the output of the selenium photocells. An Esterline-Angus 5 milli-ampere continuous ink writer was used as a recorder. The various impedances were properly matched so that the entire unit gave linear response to changes in intensity of the incident light. Figure 2 illustrates this unit.

Arterialization of ear blood. Conventional methods of heating the ear by radiant heat from the light source were employed. In addition, a method of perfusing heated air over the ear was used to study the effects of such conducted heat (superimposed over the radiant heat of the light source) upon the arterialization of the ear blood. Another method for arterialization utilized the local administration of histamine to the ear by electrophoresis as described by Matthes.⁷ One cc of aqueous solution containing 2.75 mgm of histamine acid phosphate was placed on the positive electrode (1 cm x 1 cm in size and covered with blotter paper). The positive electrode was applied to the ear, the negative electrode to the subject's leg. The current was slowly adjusted to

* We are indebted to Mr. Max D. Liston of the Perkin-Elmer Corporation, Glenbrook, Connecticut, for the design, construction, and loan of the ear spectrophotometer.

5 milliamperes at a rate governed by the subject's comfort. Too rapid a change in current produced slight dizziness, apparently due to stimulation of the vestibular apparatus. Electrophoresis was continued at this current 25 minutes on each side of the ear. A marked degree of arterial flushing was produced

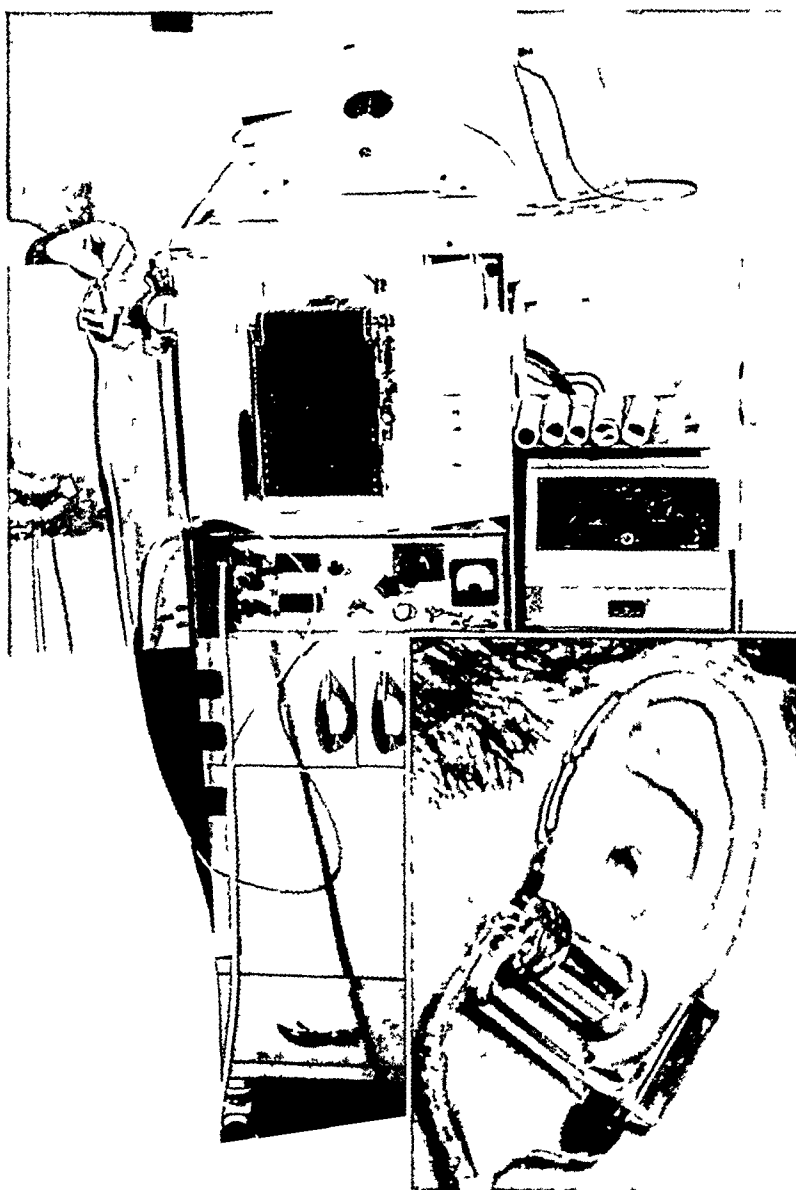


FIG 2—Recording oximeter. Galvanic apparatus for histamine electrophoresis appears in upper part of photograph. Operator holds earpiece shown in insert in left hand and the positive electrode for electrophoresis at the ear in right hand.

and maintained undiminished for two to four hours, enlargement and erythema at the site subsided after four to seven hours. No untoward symptoms or residual effects were encountered with this method.

OBSERVATIONS

Studies of the spectral transmission of bloodless ears of normal white male and female subjects revealed no interfering absorption bands of the tissue in

the spectral region between 5300 and 11,000 Å. Figure 3(A) shows a typical transmission spectrum of the bloodless ear of an adult white male. This data was obtained from the cartilaginous helix of the ear. Following determination of the bloodless transmission spectrum with the ear under pressure of 200 mm Hg, spectra were taken without applied pressure of the flushed ear while the subject breathed 100 per cent oxygen (curve B) and while the subject breathed 10 per cent oxygen (curve C).

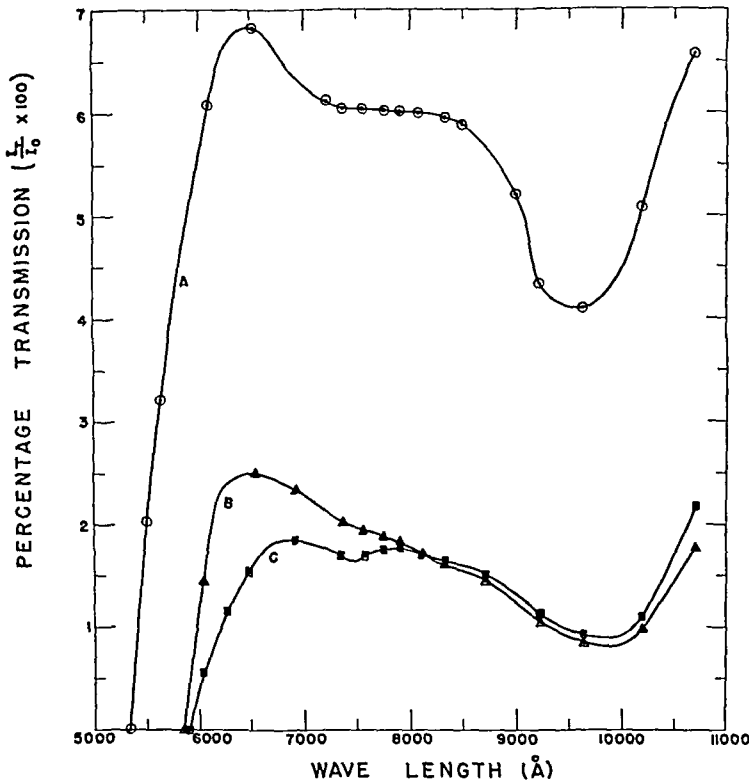


FIG 3—Transmission spectra of bloodless cartilaginous helix of normal adult white male (curve A) and of histamine flushed ear of the same subject breathing 100 per cent oxygen (curve B) and 10 per cent oxygen (curve C). A comparison of curve A with curves B and C suggests that some blood remains in the helix at a pressure of 200 mm Hg.

Transmission spectra of blood in the heated ear of a normal subject breathing air, 12 per cent oxygen, and 100 per cent oxygen are shown in Figure 4. Prior to these determinations the ear was heated by means of an infra-red lamp, and while the spectra were being taken a stream of hot air was perfused over the ear. The heat was applied to the limit of tolerance. This method of arterializing the ear blood differs from the method used in oximetry in which radiant heat from the light source is employed. The latter could not be used in experiments with monochromatic light. The transmission in the red region was highest with the subject breathing 100 per cent oxygen, lowest with 12 per cent oxygen, and intermediate with air. At approximately 7900 Å the three

FIG 4

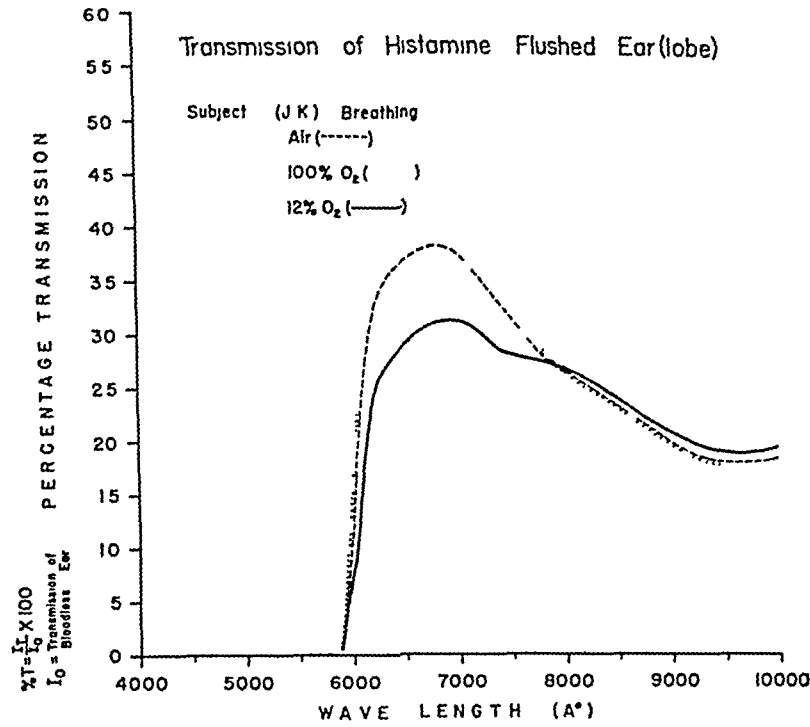
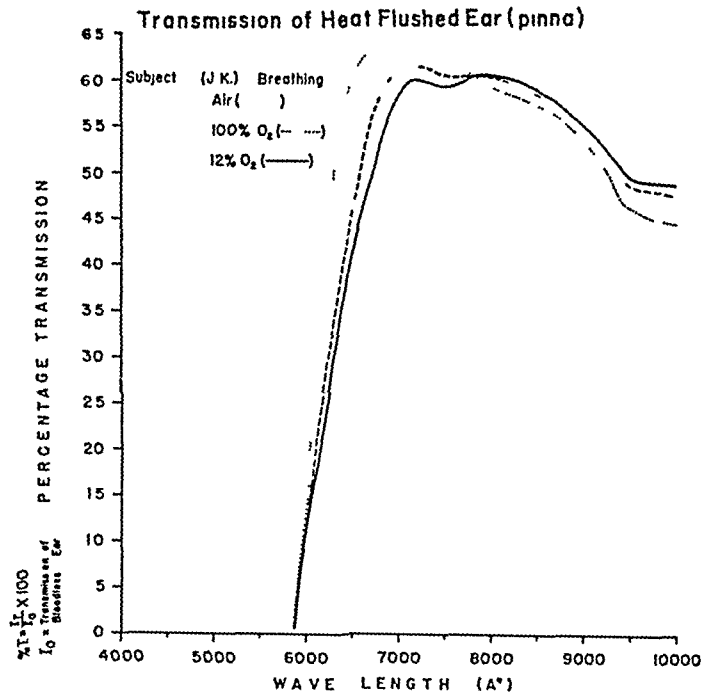


FIG 5

FIG 4 —Transmission of the heat flushed ear
FIG 5 —Transmission of the histamine flushed ear

spectra were the same. At longer wavelengths the highest transmission was obtained with the subject breathing 12 per cent oxygen, lowest with 100 per cent oxygen, and intermediate with air. Grossly these spectra resemble those of oxyhemoglobin and reduced hemoglobin. Comparison of the air curve with

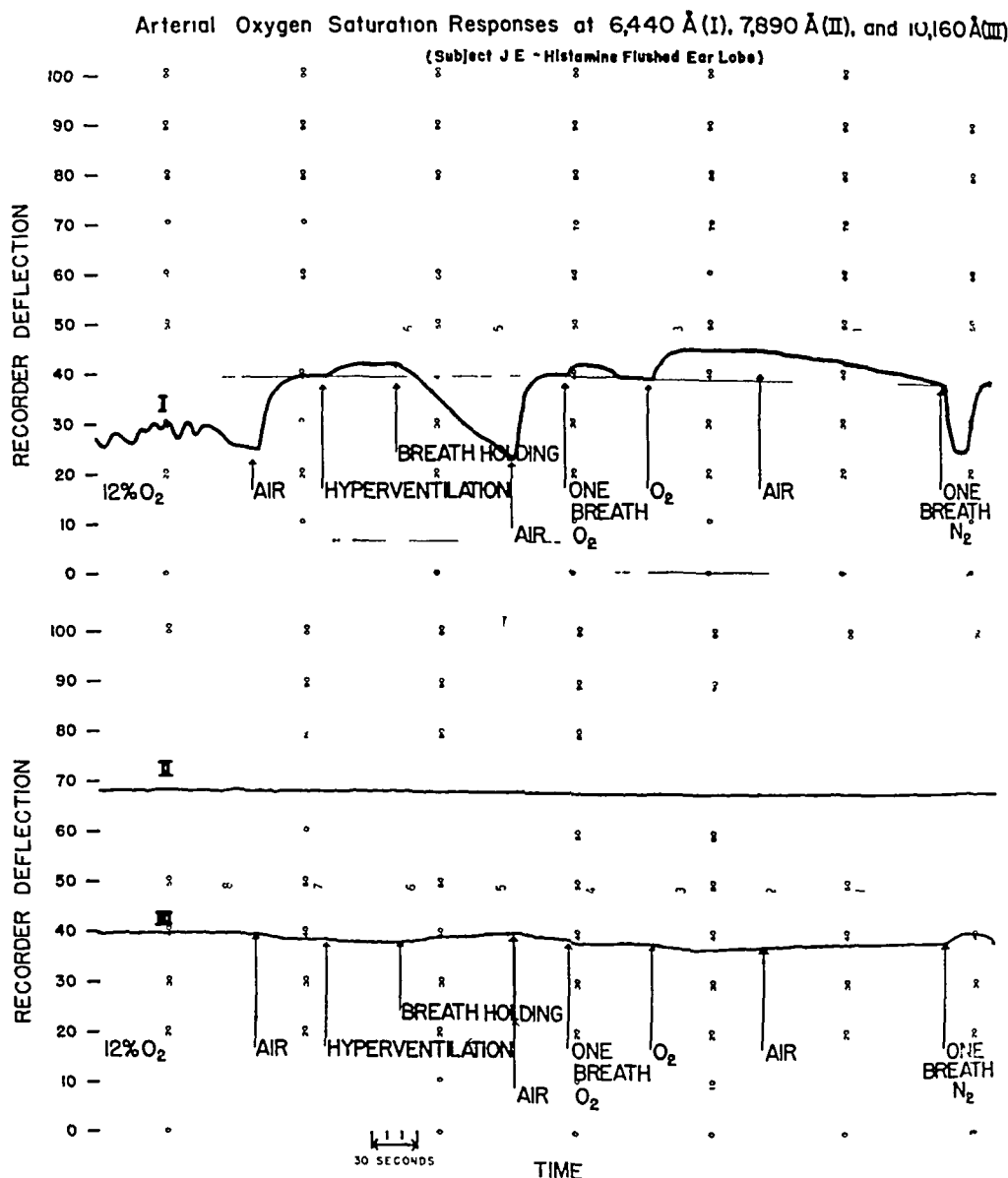


FIG 6—Arterial oxygen saturation responses at 6440 Å, 7900 Å, 10,160 Å

the 100 per cent oxygen and 12 per cent oxygen curves suggests that the ear blood was not completely arterialized. The air curve should represent a saturation of 97 per cent, the oxygen curve 100 per cent, and the 12 per cent curve 75 to 80 per cent. Actually the air curve deviates inordinately from the oxygen curve and more closely approximates the 12 per cent curve.

Further evidence for this interpretation was obtained in the same subject when the spectra were taken from the histamine flushed ear (Fig 5) Under these conditions the air curve reasonably approaches the 100 per cent oxygen curve and deviates markedly from the 12 per cent curve Thus, the histamine flushed ear contained blood more nearly arterial than did the heated ear A striking feature in the histamine spectra is the greater quantity of blood per unit of tissue as compared to the heat spectra This observation may be important in oximetry since a greater percentage change in light transmission results from a given change in the saturation Theoretically, the greater the degree of vasodilatation, the more complete would be the arterialization, assuming no change in arterial pressure The heat and histamine spectra illustrate the importance of complete arterialization of the ear blood in the oximeter measurement Variable components of venous blood in the optical path would produce error and defeat reproducibility

Figure 6 indicates transmission values at fixed wavelengths Oxygen saturation was changed by allowing the subject to breathe various gas mixtures, hyperventilate, and hold his breath The wavelengths selected to measure the resulting transmission changes were (1) in the red region (6440 Å) to obtain large differences in light absorption between oxyhemoglobin and reduced hemoglobin, (2) in the near infra-red region (at 7900 Å) to obtain identical absorption between the pigments at their "crossover" point, and (3) in the infra-red region (10,160 Å) to represent the reverse effect in absorption of the pigments at a wavelength longer than that of the "crossover" point In Curve I marked fluctuations in the transmission occurred with each respiratory cycle while the subject breathed 12 per cent oxygen When the subject breathed air the transmission value increased and reached equilibrium within 15 seconds Hyperventilation further increased the value and breath-holding produced a decrease Breathing air again duplicated the previous response A single inspiration of oxygen immediately followed by air breathing provided a transient increase in the transmission The high sensitivity illustrated by this response has not been observed with conventional oximeters in this laboratory Upon changing from air to oxygen the transmission value again reached equilibrium within 15 seconds One breath of nitrogen followed by air breathing provided a very steep decrease in the transmission value These measurements suggest that higher sensitivity could be obtained in oximetry if the red transmission were measured in a narrow wavelength band taking optimal advantage of the difference in light absorption between oxyhemoglobin and reduced hemoglobin Actually in existing oximeters this measurement has been made using a very broad spectral band (6000 through 8400 Å) which sacrifices this advantage

Curve II of Figure 6 (taken at 7900 Å) indicated no significant changes in transmission when the subject breathed the same gas mixtures, hyperventilated, and held his breath as in the previous experiment (Curve I) This observation further confirmed this wavelength as a "crossover" point between

oxyhemoglobin and reduced hemoglobin. It also indicated that under the conditions of these experiments no significant changes occurred in the total hemoglobin content of the histamine flushed ear.

In Curve III of Figure 6 (taken at 10,160 Å) the changes in light transmission produced by changes in arterial oxygen saturation were in opposite direction to the changes in transmission measured in the red region (Curve I) and of lesser magnitude.

Ideally, the two-color oximeter should provide measurements comparable to those shown in Curves I and II. The red measurement should indicate the maximal differences between oxyhemoglobin and reduced hemoglobin, the infra-red measurement should measure total hemoglobin completely independent of the oxygen saturation.

Figure 7 shows the transmission of varied infra-red filters which have been used in the oximeter. Since selenium photocells are relatively insensitive in the infra-red region an S-1 phototube was used for these determinations. The Wratten 61N filter was first used in the Millikan earpiece, Coleman subsequently substituted the Wratten 87. The modified oximeter of Wood and associates uses two thicknesses of Wratten 88A for the infra-red cell. With the selenium photocells used in this laboratory none of these filters provided an infra-red cell which was independent in output of changes in oxygen saturation. Unfortunately there is considerable variability in near infra-red response of different photocells, so that a filter affording the desired characteristics with one cell may not behave similarly with another. Empirical trial of various filter combinations resulted in the selection of a combination of Wratten filters (No. 87 in 3 layers and No. 88 in 2 layers) which fulfilled the requirement of independence from changes in oxygen saturation. The transmissions shown in Figure 7 show how the short wavelength "cutoff" of these filters is related to the crossover point of oxyhemoglobin and reduced hemoglobin. Comparison of these curves with the spectral response of a selenium photocell (Fig. 8) indicates that shifting the filter "cutoff" short of 8000 Å would provide a greater photocell output at the expense of measuring at the crossover point. Thus, infra-red filters providing a greater sensitivity with selenium photocells introduce the undesirable responses to changes in oxygen saturation. Ideally the infra-red measurement should deal only with total hemoglobin.

Figure 8 compares the spectral response of a selenium photocell to that of the S-1 phototube. At 6500 Å the relative responses of the two detectors are approximately equal, or 40 per cent. At 8000 Å the selenium response is only 3 per cent and the phototube response is 75 per cent. With some phototubes the response is 100 per cent at 8000 Å. The Wratten 29F filter has been used for the red cell in all of the oximeters in this country. There is overlapping between the spectral transmission of this filter and any of the infra-red filters. The advantages of using an S-1 phototube with better isolation of both the red and the infra-red measurements in oximetry appear promising.

Figure 9 shows red and infra-red oximeter responses to changes in oxygen saturation and to changes in ear blood volume. The latter were obtained by Valsalva maneuvers and by Mueller maneuvers, consisting of forced expiration

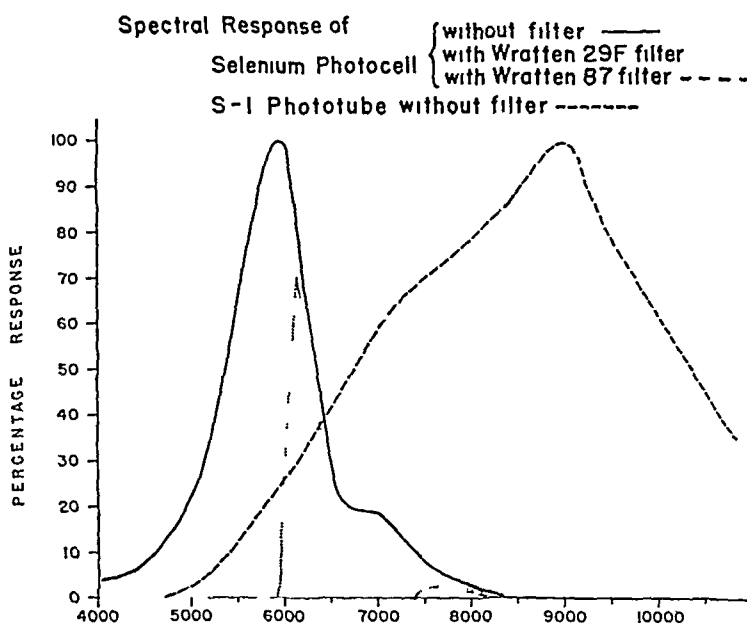
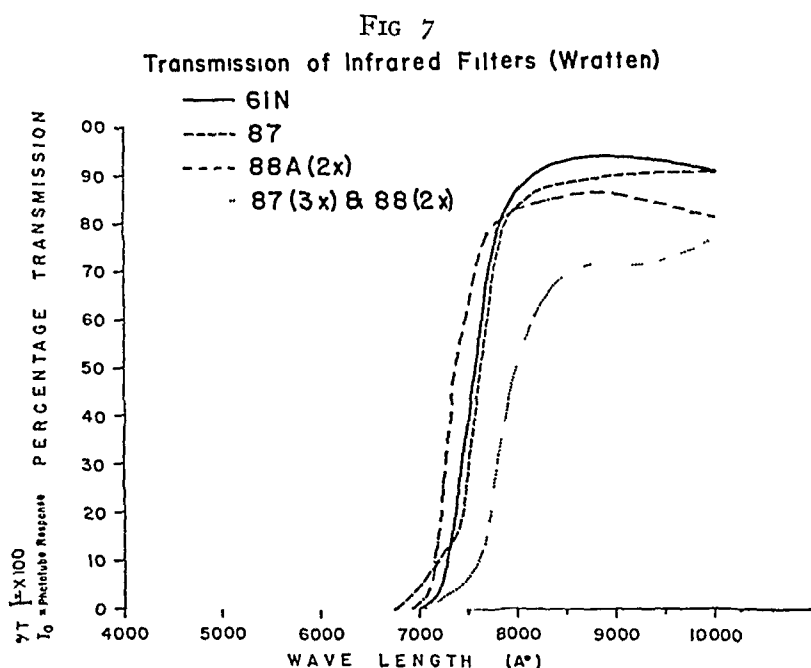


FIG 8

FIG 7—Transmission of infra-red filters

FIG 8—Spectral response of selenium photocell and S-1 phototube

and inspiration respectively with glottis closed. The unit shown in Figure 2 was employed to amplify and record the responses of the red and infra-red cells. Curve I was obtained with Wratten 87 filter; changes in transmission with changes in oxygen saturation are apparent. This effect was excluded

when the filter combination previously described was used (Curve II), however, this unit fortunately retained a comparable sensitivity to changes in total hemoglobin

Curves III, IV and V of Figure 9 compare saturation responses of the red cell (Wratten 29F) when either heat or histamine was employed to arterialize the ear blood. Curve III was obtained with a Millikan earpiece on the heated cartilaginous pinna. Note the prolonged saturation time of 120 seconds when the subject changed from air to oxygen. Curve IV was obtained with the earpiece illustrated in Figure 2 applied to the heated ear lobe. Here the responses suggest that more arterial blood was present in the optical path since greater deflections occurred with changes in saturation. Curve V was obtained with the same earpiece applied to the histamine flushed ear lobe of the same subject. Remarkably rapid dynamics were recorded when the saturation was changed, these curves actually compared quite favorably with those obtained with the ear spectrophotometer (wavelength at 6440 Å). The saturation time on changing from air to oxygen was 20 seconds. The steep decrease in transmission (Curve V) with nitrogen breathing and the rapid return of the transmission to the previous air value bear a striking contrast to the Millikan measurements upon the heated ear.

Figure 10 compares the rapid desaturation responses obtained by a single maximal inspiration of helium measured with a red cell applied to either the heat flushed or the histamine flushed ear. The breathing maneuver was that employed for the oximetric determination of cardiac output.⁵ If the pulmonary mixing of the inspired helium reduces alveolar oxygen tension to that of the mixed venous blood, the oximeter value will reach a "plateau" lasting 6 to 10 seconds, which is then terminated by recirculation. The oximeter shown in Figure 2 was applied to the heated ear lobe of a normal subject. Repeated attempts to obtain the "plateau" were unsuccessful, two of these records are shown in upper Figure 10. Upon completion of each trial when air was breathed the oximeter value did not return to the previous air normal value immediately but required at least two minutes. These prolonged responses were not associated with periodic breathing following the period of hypoxemia. These observations afford another criterion for the presence of venous blood at the site of measurement. In comparison consecutive trials were all successful when the histamine flushed ear lobe of the same subject was the site of measurement (lower Figure 10). Moreover air breathing after each maneuver was followed by a return within ten seconds to the previous air transmission values. Thus, the action of histamine had more completely arterialized the ear blood. In this application of the oximeter this source of error is of prime importance.

Experiments for evaluating the effects of heat in arterializing the ear blood may be summarized briefly. An experimental earpiece was constructed which provided for two independent sources of heating. A conventional Millikan oximeter light source was mounted in the earpiece so that it would be separated

FIG 9

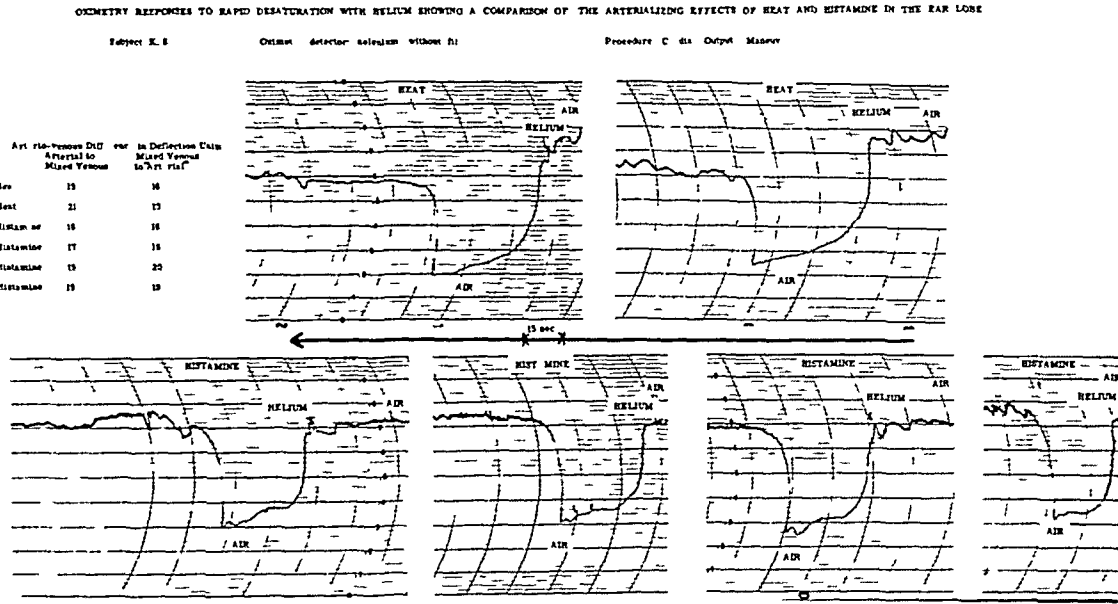
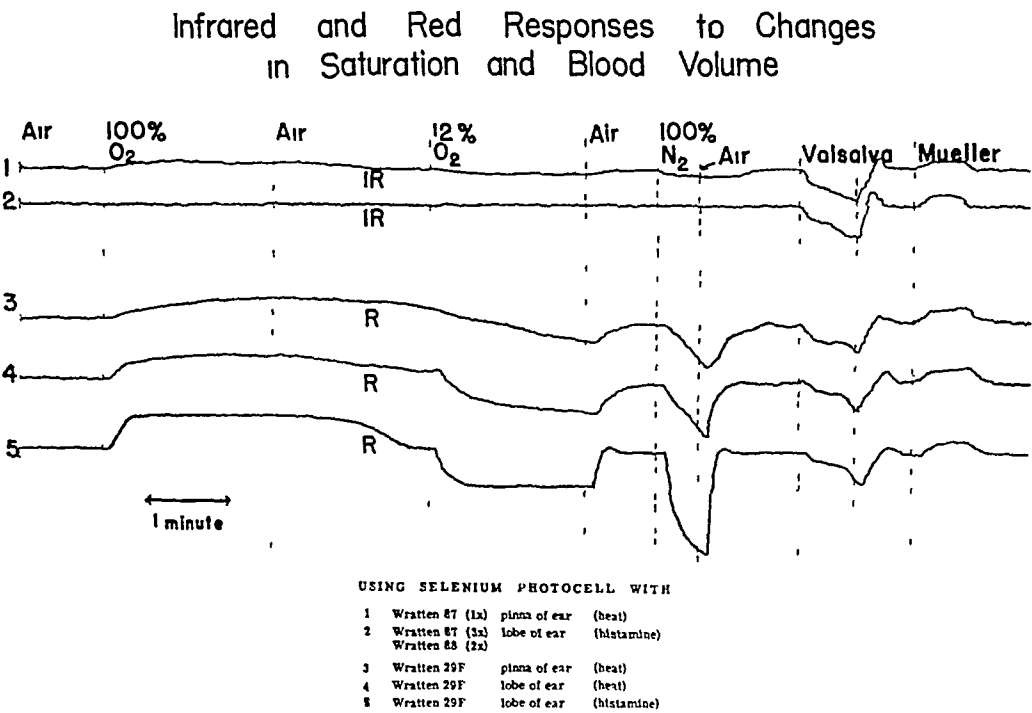


FIG 10

FIG 9—Infra-red and red responses to changes in saturation and blood volume
FIG 10—Oximetry responses to rapid desaturation with helium comparing the arterializing effects of heat and histamine

from the proximal ear surface by 3 mm, this unit provided the radiant heat which has been employed in oximetry. In addition the light source enclosure was converted into a system for circulating hot air over the proximal ear surface. In other respects the earpiece was similar to that described by Wood. Bloodless and heat flushed ear transmission values were recorded in the red and infra-red by means of the unit shown in Figure 2. The oximeter output was calculated as the ratio of $(\log R_o - \log R_n)$ to $(\log IR_o - \log IR_n)^*$ as described by Wood.² The earpiece was applied to the cartilaginous pinna of normal subjects, 15 minutes were allowed after the light source was turned on to allow "thermal equilibrium" as evidenced by a constant reading in the infra-red value, and oxygen was breathed. The decrease in oximeter output on changing from air to oxygen was comparable to that obtained by Wood. Additional heating of the ear was then started by means of the hot air perfusion method. A further decrease in the oximeter output was uniformly observed. This change, indicating an apparent increase in oxygen saturation of the blood in the optical path, continued for approximately five minutes and then the value became stabilized. Graded increases in the temperature of the perfused air over the ear produced further decreases in the oximeter output. When this value had become stable for a given temperature the administration of oxygen consistently reduced the oximeter output below that obtained by air breathing. Since this additional heating of the ear increased the arterialization of the ear blood, it is apparent that the previous heating by the light source, per se, had not afforded complete arterialization.

DISCUSSION

Evidence suggests that an absolute quantitative oximeter method may eventually be developed through the elimination of known sources of error and refinement of the measurements according to the principles of spectrophotometry. The clinical value of an oximeter of this type justifies this development. Original contributions to oximetry should be credited to Kramer^{1, 13, 15} and to Matthes^{20, 21}. Earlier studies by Nicolai²² dealt with the light transmission changes when tissue was occluded as a measure of the reduction time of oxyhemoglobin. Kramer's one-color unit, measuring transmission in the red region, was designed to fit around the intact artery of the dog. It consisted of a small tungsten light source, a selenium photocell, and a galvanometer. He was able to obtain an agreement within 1 per cent of the saturation values determined by chemical analysis. Matthes²¹ modified the method for determinations upon the transilluminated human ear and added a second measurement in the near infra-red to provide an index of changes in total hemoglobin in the optical path. His device consisted of a light source, a selenium photocell and galvanometer for the red measurement, and a phototube and galvanometer

* R_o and IR_o represent the red and infra-red bloodless transmission values, respectively

R_n and IR_n represent the red and infra-red "normally flushed" transmission values, respectively

for the infra-red measurement. Subsequent modifications of the oximeter have incorporated this two-color principle.

Goldie²¹ introduced the correction factor for the light absorption contributed by the bloodless ear tissue. The latter was measured by occluding the ear tissue with a movable transparent plunger in the earpiece. His was the only instrument to be described in which the indicated oximeter value represented the ratio of $(\log R_0 - \log R_n)$ to $(\log IR_0 - \log IR_n)$. The latter calculation was performed as a function of electrical circuit and a specially devised ratiometer.

Millikan's oximeter²⁴ indicated the saturation value as a simple difference between the red and infra-red transmissions, $(R_n - IR_n)$. The log-ratio relationship was abandoned to obtain a simple qualitative instrument for use in altitude physiology. Preliminary adjustment of the oximeter value to that estimated by the operator limited the clinical usefulness of Millikan's device. In patients with arterial hypoxemia, repeated sampling of the arterial blood for chemical analysis was necessary. Without these calibrations for each procedure the Millikan oximeter served merely to indicate changes in the patient's arterial oxygen saturation. Hemingway and Taylor²⁵ adapted the Millikan instrument for continuous ink recording by means of an amplifier¹⁹ and recorder similar to that previously described (Fig. 2). The oxyhemograph of Haitman, Behrmann, and Chapman²⁶ is a similar recording instrument. These modifications differ from the original Millikan device primarily in the means used for recording the oximeter value.

The recent work of Wood and associates^{2, 27} has revived the bloodless ear tissue correction and the log-ratio relationship employed by Goldie. Their work represents the first major attempt to make the oximeter measurement an absolute determination, permitting estimation within ± 5 per cent of a patient's arterial oxygen saturation, regardless of the degree of arterial hypoxemia.* The evidence of the reliability of their modified oximeter, based on extensive Van Slyke calibrations, suggests that this approach is valid, and that further refinement in the method should lead to higher accuracy.

The studies now in progress which have been described in this preliminary paper represent the first attempt to evaluate the problems in oximetry by means of spectrophotometry. On the basis of these data the selection of optimal wavelengths for the red and near infra-red oximeter measurements may be made. The spectra of the ear reveal no interfering bands of absorption due to tissue in these regions. The use of monochromatic light in the source would appear to offer a greater degree of sensitivity. Although the mathematical relationship, which appears to be valid, relating the light transmission measurements to the oxygen saturation is somewhat complex, it would offer a great convenience in the clinical oximeter to perform this calculation by means of an electronic circuit. Improved components for the instrument which require

* Calibrations in this laboratory of a two-color oximeter similar to that of Wood and Geraci²⁷ have shown a comparable degree of accuracy.

development may resolve the colorimetric oximeter into an essentially spectrophotometric apparatus

Failure to obtain complete arterialization of the ear blood represents a major source of error and variability. This factor may involve more than an optimal degree of vasodilatation if the application of the earpiece is such that blood is trapped within the optical path. It would appear that both inadequate arterialization of the ear blood and a limitation of blood flow across the optical path contribute to the prolonged saturation dynamics obtained with the Millikan earpiece. Thus, the saturation time when normal subjects change from air to oxygen has been reported by Fowler and Comroe⁸ to average 120 seconds. This agrees with the observations in this laboratory when the Millikan oximeter was used. Wood, Taylor, and Knutson¹⁰ have reported an average of 46 seconds for the saturation time, using the modified oximeter. As indicated in this paper this response is of the order of 15 to 30 seconds when the measurement is made upon the histamine flushed ear. In applications of the oximeter which relate to the dynamics of gas exchange in the lungs it is of prime importance to obtain arterialization of the ear blood.

Recently Wood and associates^{6, 10} have reported evidence that the heating technic employed in the modified oximeter earpiece does afford arterialization of the ear blood. * Since the degree of heating in this unit is comparable to that obtained with the Millikan earpiece it would appear that some additional feature in the method of Wood excludes the venous blood from the optical path. The application of the earpiece to the ear at considerable pressure and the initial exclusion of all blood from the optical path by inflation of the pressure capsule may well eliminate the venous component. It should be pointed out that the entire ear is not heated by the light source, so that the blood from adjacent unheated capillaries which is drained by large veins traversing the optical path is apparently the non-arterialized blood in question. Observations described above indicate that the use of heat to arterialize the ear blood is subject to variability greater than that encountered when histamine electrophoresis is employed. If heat is to be employed in oximetry, more data are required to determine the critical threshold for optimal arterialization. Establishing a standardized technic in this regard is essential. Histamine electrophoresis offers the advantages of a more stable local vasomotor state and an increased amount of blood per unit of tissue. The latter factor provides a greater measurable change in light transmission with a given change in the arterial oxygen saturation.

Among other potential sources of error which have not been evaluated is the way in which the two photocells are mounted in the earpiece. In both the Millikan and Wood earpiece the red cell is a narrow central area on either side of which the larger infra-red cells are placed. Whether both cells can view the same sample of blood and ear tissue in the optical path is questionable.

* Comparison of heat and histamine arterialization reported recently by Wood and colleagues has not indicated a significant difference in the two methods.

The fact that the vascularization of the cartilaginous pinna is not one of fine homogeneity further suggests that this factor deserves attention. Another source of error which may be eliminated is the variability in red and infra-red energy emission due to changes in the voltage applied to the light source. Critical control of lamp voltage to maintain a constant filament temperature is important.

The development of a quantitative oximeter is, of necessity, a long range program. Construction of improved miniature components for the earpiece providing the ideal spectral characteristics is a project in itself. Progress has been made in the electronic calculating circuit to permit the recording of the saturation value representing the ratio of $(\log R_0 - \log R_n)$ to $(\log IR_0 - \log IR_n)$. Finally, extensive and time-consuming calibrations must be performed to determine the limits of accuracy of a new oximeter.

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DISCUSSION—DR JOHN H GIBBON, JR, Philadelphia, Pa I assume that a good many of you, like myself, have felt a little at a loss concerning some of these curves of the wave length of light However, I think the work that Dr Elam has done is very valuable

We have been trying to improve upon the Millikan oximeter, which is now available Dr Miller, of our department, has constructed an oximeter which differs from the Millikan and which we think is better We have used this instrument in some 20 intrathoracic operations Because the patients are breathing a mixture of pure ether and oxygen, we find that their blood is completely saturated with oxygen during the course of the operation, and we find the instrument of little clinical value except in the induction phase of the anesthesia when the saturation may drop off and also in the immediate postoperative period when the anesthesia is discontinued

Thus, immediately preceding the anesthetic and in the immediate post-anesthetic phase, I think the oximeter, particularly these improved models which Elam and others may develop, may be of considerable importance

I hope they will be able to develop one which gives a linear deflection of the writing point with changes in saturation, instead of a larger deflection of the writing point as the upper limits of saturation are reached

I assume Dr Elam has checked the plateau, observed when breathing helium, by a catheter introduced into the right auricle directly measuring the saturation of the mixed venous blood I assume he did not have an opportunity to tell us about that

Another difficulty which we have encountered in the use of the oximeter has been that deflections occur when the patient's position is shifted on the operating table. When a patient is shifted from the horizontal to the head-down position a considerable deflection of the writing point occurs, which is unfortunate.

If we could develop an instrument which would continuously record the CO_2 tension of the arterial blood, we would have something much more valuable. Unfortunately, the physicists don't seem to be able to produce such an instrument.

DR JAMES O. ELLAM, St. Louis, Mo. A linear oximeter scale would be more convenient for accurate reading, particularly in the lower saturation range. The alinearity of the Millikan compensating circuit oximeter is a result of taking a simple difference between the red and infrared transmission values. This relationship gives a range from 90 to 100 per cent saturation, which is approximately three times that between 50 and 60 per cent saturation. An electronic circuit for computing the logarithms of the red and infrared values and then taking their ratio would probably provide a scale for the oximeter that would be linear. This complex circuit may not be practical for general clinical use. Recently we have obtained evidence that a simplified circuit might be useful in providing an oximeter scale which is approximately linear.

Right heart catheterization studies to confirm the validity of the oximeter value for the mixed venous blood have been postponed until the accuracy of the oximeter would make such an evaluation worthwhile. Dr. Earl Wood of the Mayo Clinic has obtained evidence that the ear oximeter value during the "plateau" of the cardiac output determination is duplicated by measurements made simultaneously with a whole blood oximeter coupled to the radial artery. This method is theoretically valid only when a definite plateau is recorded within one circulation time following the inspiration of helium. When this does occur, one must assume that mixed venous blood is perfusing the lungs without change in oxygen content.

We have also observed the oximeter responses to changes in posture to which Dr. Gibbon referred. With the Millikan instrument these effects may be artifacts due to slippage of the earpiece or to actual changes in the amount of venous blood in the ear at the site of measurement. In severe cardiac patients such responses may be real. With our present technique in which histamine is used to arterialize the ear blood, changes in posture of normal subjects does not produce these oximeter responses. It should be possible with the improved oximeters now in development, to interpret these effects, when they are observed in patients, with greater assurance that one is not dealing with instrumental artifacts.

THE EXPERIMENTAL STUDY OF FLASH-BURNS*

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THE WEAPONS OF MODERN WARFARE have produced a thermal lesion from a very brief exposure to radiant heat of high intensity that has been called a "flash burn" This was first encountered in a mass form during the bombing of Pearl Harbor in December 1941²² Eckert and Mader,⁶ writing of the casualties from this say "only exposed surfaces were burned, even an undershirt or shorts appeared sufficient to prevent areas covered from being burned" No third degree burns were seen The armed forces continued to encounter the flash burn throughout the war, but it was not until the Japanese casualties of the atomic bomb explosions at Hiroshima and Nagasaki were studied that the tremendous implications of the problem became apparent Burns of all degrees of severity were observed there

LeRoy¹⁵ estimated that of the atomic bomb casualties in Japan 65 to 85 per cent were burned, 70 per cent sustained wounds, and over 30 per cent had irradiation injury Others have estimated that over three-fourths of the casualties were from mechanical or thermal injuries Those near the center of the explosion were, to use the words of Parsons,²¹ "killed three times" by blast, heat, and irradiation But the injurious effects of the blast and heat extended beyond that of the irradiation, hence the larger number of casualties which they created The heat producing these burns was tremendous, and some individuals 2.5 miles (3 Km) from the center of the explosion were sufficiently burned to require treatment The sequelae were many and prolonged¹⁵ and the incidence of keloids was high²

The physical mechanism producing these high intensity burns is quite unlike that causing the ordinary burn seen in civil life It is reasonable to suppose that its effect upon the organism will also differ, and that the local lesion, clinical course, and prognosis will not be the same A thorough search of past literature, a survey of work done under OSRD contracts, a review of current work on burns, and personal inquiry, indicate that this problem has not received adequate attention, either from a basic or clinical standpoint The clinical problem of the management of thousands of severely burned casualties is enormous We have recently seen how a few hundred burn cases strained the medical facilities of Hartford or Boston Imagine this situation multiplied 200 times! Obviously, the methods used in present practice are too

* This paper is based on work performed under contract with the United States Atomic Energy Commission at The University of Rochester Atomic Energy Project, Rochester, New York Read before the American Surgical Association, St Louis, Mo., April 22, 1949

elaborate, for they would have required at Hiroshima trained medical personnel in excess of the population of New Haven, materials and supplies greater than the gross tonnage of a Liberty Ship, and tank cars of blood. In the solution of this baffling clinical problem it appears obligatory first to know the characteristics and effects of "flash burns." What do they do to the skin? How do they affect the organism, and how can this effect be modified? What is their clinical course and how can it be altered by treatment? How lethal are they and what factors influence their mortality? To try to answer these and other questions one must produce and study the lesion experimentally. This report deals with laboratory methods of creating "flash burns" and the lesions produced.

REVIEW

Experimental burns have been produced by many individuals in as many different ways. Leach, Peters and Rossiter¹⁴ caused a very satisfactory experimental, moderate temperature burn, using a vessel through which water of a known temperature circulated. They found that an application of 70 to 80° C of only 10 to 20 seconds duration produced severe "scabbing." Intervening temperature and exposure times produced roughly proportional injury. Microscopic examination of the tissues showed degrees of cellular disintegration, with mild burns and heat coagulation with the more intense ones. Among other conclusions they found that severity of the burn was dependent on the *duration* and the *intensity* of the stimulus.

In amplification of this work, Mendelsohn and Rossiter¹⁷ made subcutaneous temperature determinations, using a copper-constantan thermocouple. They found that a rather prolonged exposure of 45 to 60° C was required to elevate the subcutaneous temperature. The temperature rose rapidly in the first two minutes, then levelled off gradually at four minutes, dropping slowly after the discontinuance of the burning iron application to nearly a normal range in the next six minutes. They made an excellent histopathologic study of cutaneous thermal injury in the guinea pig.

Working along the same lines, but with more adaptable equipment, Henriques and Moritz¹² sought to define the physical factors determining the transfer of heat energy through the skin. It was found that the caloric up-take rate of the skin, as measured by thermocouples at the dermis-fat interface, during the first 0.2 minute was about six-fold greater than the average caloric up-take during the ensuing 7 to 10 minutes. Maintenance of the skin surface for five minutes at 45° C resulted in heat saturation of the dermis. However, with skin surface temperatures of 50 to 70° C, edema fluid accumulated at the dermis-fat interface, thus cooling the dermis within and decreasing the effective thermal conductivity by some 15 per cent. The epidermis, it was calculated, became heat saturated within 0.5 to 1.0 minutes heat exposure, when brought immediately to the desired temperature at the surface.

The further establishment of the importance of *time-temperature* relationship was developed in the comparative study of burns on human and pig.

skin Using transepidermal necrosis as an end point, it was found that 44° C for six hours would produce an effect similar to 51° C for two to six minutes When the surface temperature was lower than 44° C, there was a rapid decrease in the rate at which burning occurred, and the time-temperature curve was found to be asymptotic in the direction of the time axis However, when the surface temperature was greater than 51° C, the exposure time was so short that during most or all of it the deeper layers were in the process of being brought to, rather than being maintained at, a state of thermal equilibrium with the surface Thus the time-temperature curve above 51° C was found to be asymptotic in the direction of the temperature axis

Moritz¹⁸ in studying the pathogenesis of cutaneous burns, concluded that the quantitative results of a short exposure of high intensity might be similar to those of a long exposure of low intensity However there were likely to be qualitative differences Hyperthermia of high intensity resulted in a coagulative type of necrosis, in which the dead tissue was not autolyzed but rather disposed of by sequestration, while that of low intensity resulted in a noncoagulative type of necrosis, the dead tissue being autolyzed and readily susceptible to organization It was possible, by using intense exposures of around 0.5 second duration, to carbonize the superficial shreds of stratum corneum without causing sufficient subsurface rise in temperature to damage the basal layers of epithelial cells, or to cause perceptible vascular reaction Again, protracted vascular reactions were noted, without noticeable harm to the epidermis

The findings of Henriques, Moritz *et al* are fundamental for any study of thermal injury The demonstration of the time-temperature relationship and its importance in the production of different types of burns, forms a foundation for the further study of these types of burns The observation was made that so brief an exposure to flame temperature is required to raise the epidermal-dermal junction to "cell-killing" level, that anything capable of impeding heat transfer to the skin, "would be sufficient to make the difference between burning and absence thereof" Even a thin film of moisture on the surface of the skin would be sufficient to prevent a burn at near threshold levels¹⁸ The continuation of this investigation will in effect be the extension of the curve (Fig 1) towards the time axis, and away from the temperature axis

METHODS

A flash source must have the characteristics to produce burns, and yet be controllable, and accurately measurable It seemed that at least the following criteria should be met to produce an ideal flash

- 1 Transient duration on the order of 0.1 second
- 2 Extremely high intensity, of a known and possibly variable nature
- 3 A known or obtainable spectral distribution
- 4 Safety and convenience of handling

The complicated nature of heat transmission makes it more practical to produce the burn by radiant heat. This also simulates field conditions. So attempts have been made to eliminate flame, or direct contact sources, *per se*. By confining the heat transmission to radiation alone, an accurate knowledge of the spectral distribution of the source is required, as well as its emissivity in its flashing state. Since the skin can be considered as behaving in the same manner as a perfect black body at 300°K ,¹⁰ absorption of radiations from such a source can be considered to be complete.

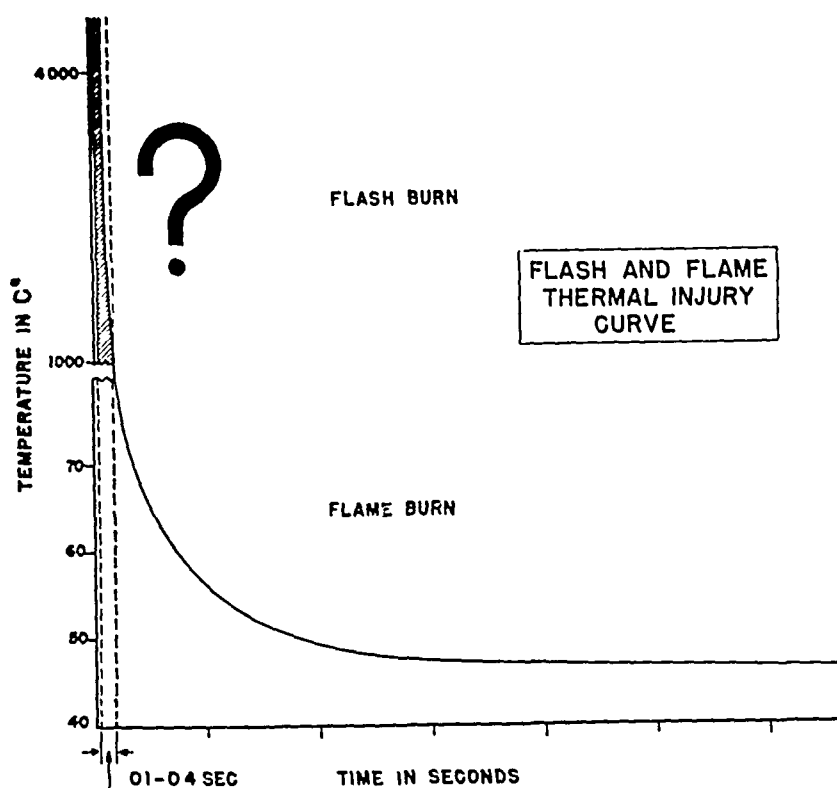


FIG 1—The curve of time-temperature thresholds of epidermal injury has been drawn from Henriques' results to include the "flash burn" range which is under investigation. Physical measurements in this area are difficult, but in general the experimental data obtained confirms that derived from computation.

Accordingly, a search for possible sources was begun. The agents tried are listed in Table I. Measurements of the duration, intensity and spectra of the various agents were gathered largely from the literature. Measurements under the experimental conditions are being made. Three general principles were tried: (a) the release of electrical energy from a bank of condensers to create a flash, (b) the creation of a constant high intensity source which is directed upon the target for known intervals by means of a shutter or trip mechanism, and (c) the use of substances that burn rapidly with an intense flame. (See Table I).

Anderson in 1919¹ described a method of exploding or burning a copper wire placed between two electrodes which were connected to a bank of condensers. Edgerton⁷ used a similar arrangement for testing xenon photo-

TABLE I—A Summary of Various Sources, Their Physical Characteristics, Effectiveness, and Complications

Source	Duration Seconds	Approximate Temperature C	Burn Produced	Complication
(FT14) Electric discharge (xenon filled) Flash tube ⁷	0.002	6300	None	Unable to focus energy
Exploding wire ¹	0.00001	20,000	None	Unable to focus energy Too brief Blast wave
Thermite ⁵	Variable	3500	Not tried	Spatter Low intensity Handling difficulty
Gun powder ⁹	To 1.0	3000	Failed	Low intensity radiation
Magnesium ²³	0.36	3500	Severe	Smoke
Carbon arc ¹⁵	Constant	4000	Severe (Constant)	Small area burn

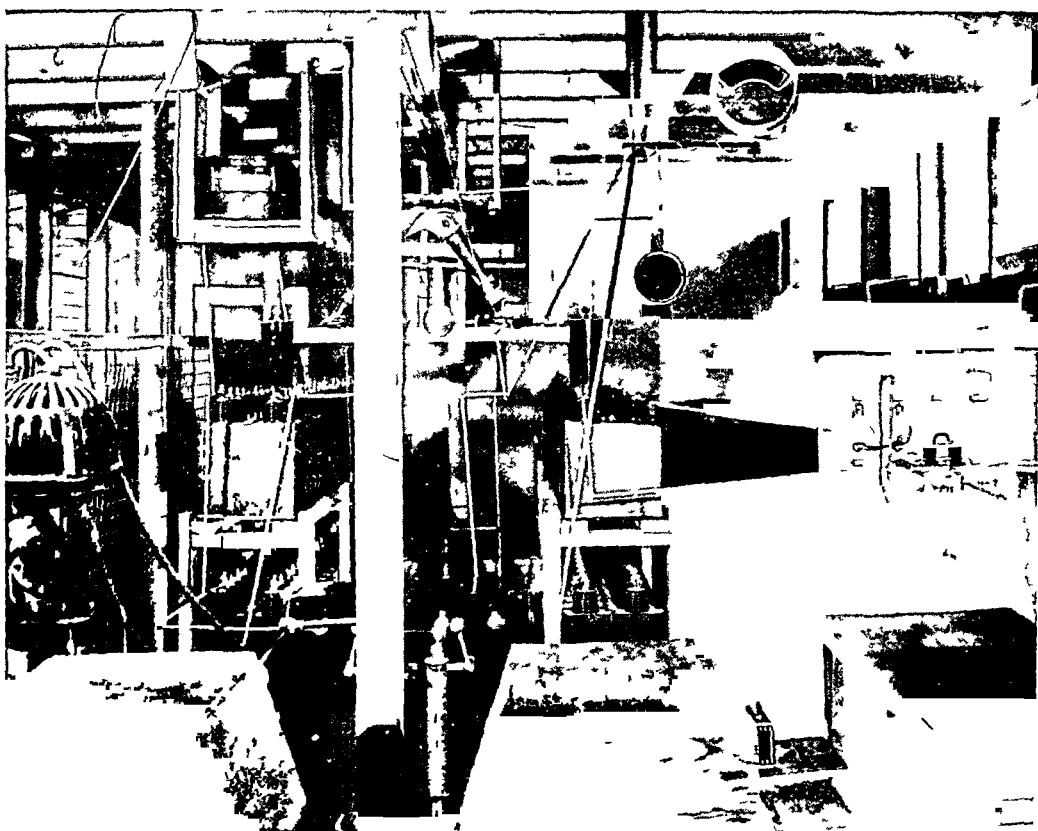


FIG 2—The bank of condensers is connected to the xenon filled flash tube (F T 14) of Edgerton. This method did not cause burning.

graphic flash tubes. Our condensers had a capacity of 64 microfarads and were charged to 25,000 volts (Fig 2). Neither of these methods caused burning. The exploding wire generates temperatures in the range of 15,000 to 20,000° C, but this is so transient, in the order of 0.0001 sec, that injury does not occur. The inability to focus this energy and the blast wave produced are additional disadvantages. The Edgerton xenon filled flash tube produces approximately 6300° C in 0.002 sec with 10,000 volts at about 16 microfarads. Efforts to magnify this by using 20,000 volts with 32 microfarads resulted in blowing out the flash tube. Burning by an electrical arc jumping across a gap was not tried. Flash burns are occasionally caused by means of an arc in the electric power industry but the intensities are greater than those produced in the laboratory.

Archimedes, by burning the fleet of Marcellus,⁴ demonstrated the possibility of focusing heat with a concave reflector. Using this principle, the energy from a carbon arc source could be brought to a focal point and the intensity, here 4000° C, largely reproduced.¹ A timing device must then be added to the apparatus to limit the exposure. We have used a rotary type shutter as shown in Figure 6, or a car carrying the animal across the focal point at a known rate. The former method gives a "spot" burn whereas the latter results in a strip of burned skin across the side of the animal. This is a relatively precise method, capable of being controlled, which is very useful in observing the local changes produced but has the disadvantage of injuring only a relatively small area of the total body surface.

A variety of substances that burn quickly with a hot flame were considered, of which gun powder, thermite, 100 octane gasoline and magnesium were studied. The assistance of the Ordnance branch of the Department of the Army was sought, and several arsenals were visited. Plants of the photographic industry, and the electrical industry dealing with illumination were also visited. To date, magnesium has been found to be the best source of this type. It is much more easily controlled and handled than others, gives a high intensity in a short time and has as its only disadvantage the production of smoke. We have detonated as much as three pounds of magnesium powder without disaster. A contrasting example is thermite, which causes extreme spatter of hot particles (Fig 3), giving contact burns that confuse the experiment. It is also dangerous and difficult to handle.

Fauley and Ivy⁸ devised a small brass cannon, which would spark fire aliquots of 0.5 Gm of magnesium at "targets," such as filter paper, rabbit skin, and the forearms of human subjects. At a distance of 24 cm from the maw of the cannon the temperature was estimated at 1,000 to 1,500° C, while at the mouth of the device it was about 2,600° C. An undershirt served to protect the skin against the burn, and an ointment of 50 per cent titanium dioxide prevented the flash burn.

We used a standard photographic flash powder, practically pure mag-

* We are indebted to Dr. Rudolph Langer for assistance with this apparatus.

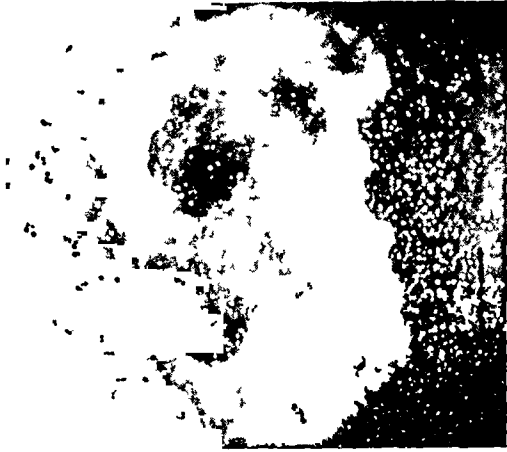


FIG 3



FIG 4

FIG 3—Burning thermite, with or without magnesium added, results in widespread dissemination of molten iron particles which complicate the experiment by contact burns. Thermite is also difficult and dangerous to handle, has a relatively slow rate of combustion and is not a suitable source for producing flash burns.

FIG 4—The early stage (about 1/30 sec.) of burning magnesium showing the shape of the flame. The transformer igniter and shielded box containing the anesthetized experimental animal are also shown.

nesium. Various methods of firing were tried, the most dependable being a high tension electric spark resulting from 110 v, 60 cycle A C current being passed through a GE type K 916 x-ray transformer, connected in series with a resistance coil used as a ballast. It was necessary to do most of the firing in the open, because of the large amount of smoke generated by the combustion of the agent.



FIG 5—A later stage of burning magnesium which demonstrates the size of the flame and the smoke produced. Magnesium is a satisfactory source to produce flash burns.

High speed motion pictures were taken of the flash, from which the duration was computed. For 124 Gm the flash duration was about 0.338 second (Figs 4 and 5). From these same films it was found that when the magnesium was burned on a flat surface of fire-resistant material, the flame and flash seemed to spread diffusely in a hemisphere about the source. However when it was placed in a saucepan, with upward sloping walls, the flame was seen to go up at an angle corresponding to the angle of the pan edge.

Preliminary studies of the flash duration made with a phototube pick-up device recorded on a cathode-ray oscilloscope, paralleled the motion picture findings. Radiation

calorimetric studies using various black-body receptors as well as indicators, are in the phase of development

From the work of Moitz, *et al*²⁰ the swine was shown to have a skin very similar in structure and physiologic reaction to that of the human being. Therefore, the pig was chosen as the standard experimental animal, though some experiments have been done on dogs, rats and rabbits. Young Chester white pigs were chosen, about two months old, with weights of 8 to 15



FIG 6—A 24-inch Army carbon arc searchlight is directed at a concave reflector which brings the focal point into the range of a high speed, electrically controlled, flash producing shutter. A car can also be used to traverse the focal point at a known rate.

Kg. These were well anesthetized with veterinary nembutal given intraperitoneally, or intravenously into the superior vena cava³. One side of the animal was closely clipped. The clipped animals were placed in a box, one side of which contained perforations. Through these perforations a variable area of the lateral surface of the pig was exposed. This surface contained skin of approximately the same thickness, and was fairly smooth. The distance and the amount of magnesium were varied at first but later a standard experiment was set up in which 124 Gm of magnesium was used with the box at 30 cm from the source.

Immediately after the flash the burns were observed, measured and photographed with 35 mm Kodachrome, panchromatic, or infra-red film. The areas were biopsied at various periods of time, ranging from one hour to two weeks, special emphasis being placed on the 1, 6, 12, 24, 48, and 72 hour periods. Usually no more than one biopsy was taken from each burn and it was so taken as to include a generous portion of normal skin on either side. The sections were fixed in Bouins solution and stained with hematoxylin and eosin. Ninety burns have been studied in this way.

The burns received no treatment. The animals were kept on their diets of commercial pig feed throughout. If one died as a result of anesthesia (which was often the case early in the work), a complete autopsy was done, including histologic examination of all burned areas.

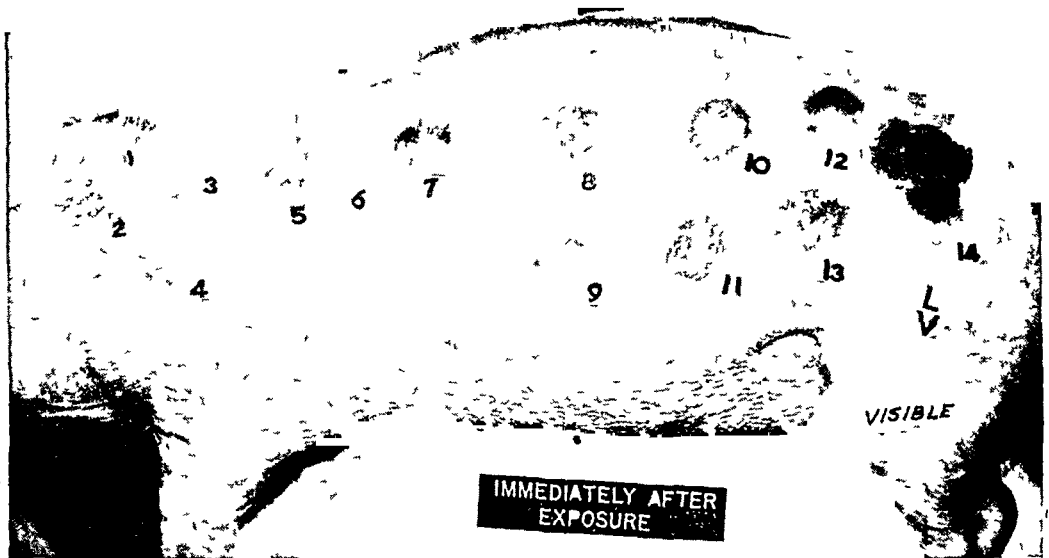


FIG 7—Small circular burns produced immediately after exposure to 124 Gm of burning magnesium at 30 cm. These occur through 3.5 cm holes bored in the side of the animal box.

RESULTS

Theoretically, the rapid exposure to intense radiant heat should change the histologic picture, for there is not time for reflex vasodilatation from warming nor from the axone reflex. This prevents the cooling effect of blood in dilated capillaries. The rapidity of the injury should not allow lateral diffusion of heat, so making the margins abrupt. This same speed might also prevent the cooling at the dermis-fat interface, thus allowing deeper penetration. In general these theoretical considerations were confirmed by observation.

The severity of the burns produced varied with the distance of the skin from the source, the amount of energy used, and the anatomical location of the burn area. In the pig the mild lesions were characterized by an erythema

which developed within the first few hours, deepening in color, and becoming tan or brown over the next few days, and finally disappearing within a week with perhaps a fine scaling of the surface

The moderately severe lesions demonstrate a peripheral flare. This flare subsides within one hour, leaving a ring of erythema about a central gray-white area of dry, cutaneous necrosis. The erythema again deepens in color, subsiding within a week. The central area also deepens in color and becomes thickened and raised by 24 hours. The edema reaches its peak by 48 hours,



FIG 8—A burn 10.5 x 15.0 cm in size produced through a larger port in the animal box by burning 124 Gm of magnesium at 30 cm distance

then subsides, giving way to induration and later to a flat, brown crust covering the burn (Figs 7 and 8). The crust remains adherent to hairs which have grown out, but it finally drops off in seven to ten days. Occasionally, vesicles are present in the central necrotic area immediately after the burn, or the epidermis may be separated entirely, leaving a raw dermal surface exposed.

Histologically, the flash burn presents several interesting features not noted in the moderate temperature burn. The common type (moderately severe, produced by 124 Gm of magnesium burned at 30 cm from the skin) presents a shredded stratum corneum. The epidermal transition from

burned to normal epithelium is abrupt (Fig 9) and often accompanied by epidermal-dermal separation at the line of juncture. The unburned epidermis is basophilic, the cells of normal architecture (Fig 10), and immediately adjacent, the burned cells are eosinophilic, present nuclear pyknosis and cytoplasmic vacuolation. The burned cells run the gamut of types described by Leach, Peters and Rossiter. Various degrees of dermal-epidermal separation are present throughout, with attachment by elongated tonofibrils in some areas. A similar abrupt demarcation of burned from normal epithelium is seen in the skin crypts and the hair follicles with deeper injury. The dermis reflects the depth of the penetration by a coagulation of the fibrils, with some fragmentation appearing later. These changes are less striking, and so are harder to detect.

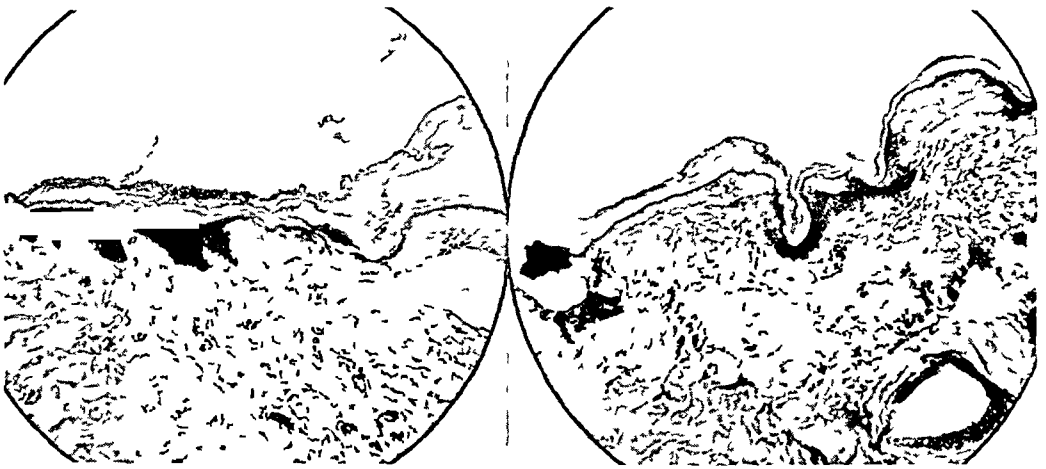


FIG 9

FIG 10

FIG 9—Biopsy immediately after burning which shows the abrupt lateral delineation of the injured epidermis and epidermal-dermal detachment $\times 65$

FIG 10—Biopsy 12 hours after exposure showing sharp horizontal demarcation through a hair follicle and mild upper dermal coagulation $\times 65$

In the sections, the edema is manifested by a loosening of the dermal collagen fibrils, this appearing about six hours after burning. Polymorphonuclear leukocytic infiltration appears simultaneously. By 24 to 48 hours, both phenomena are at a maximum, fading off thereafter, to disappear entirely in the milder lesion by the fifth day.

Healing is fairly rapid in the pig in the mild and moderately severe burns. Re-epithelialization begins at 48 hours and generates from surviving epithelium of hair follicles, crypts and lateral margins. It is completed by ten days. The thermally damaged epithelium is undercut by the growing epithelium and the former shed as a dense sequestrum. This eschar remains, covering the lesion, several days after complete re-epithelialization has occurred. Only rarely was granulation seen in the experiments.

In the more severe transcuteaneous burns, demarcation is not as marked laterally or in depth. The epidermis, dermis and underlying fat have a fixed coagulated appearance. The characteristic leukocytic boundary and healing

by granulation seen in lower temperature burns are present in this degree of flash burn. It is our impression that if the injury penetrates deeply, its horizontal nature may destroy all epithelium in crypts and hair follicles, leaving no epithelial islands for regeneration.

DISCUSSION

The severity of the flash burn is a rough index of the intensity of the burning stimulus, and as such, is governed by the laws of energy transfer. Severity varies inversely as the square of the distance of the skin surface from the source. It varies also with the intensity of the source, the thickness of the skin and with the curvature of the cutaneous target exposed to the source.

The most striking characteristics of experimental flash burns are found in the histologic picture. Most remarkable is the abrupt and diagrammatic demarcation between burned and normal skin. The normal, basophilic epidermal cells change, on a straight line, to the acidophilic burned cells which have all the characteristics of thermal injury. In the deeper skin this demarcation is at the burn border, in the crypts and hair follicles. It is present in the dermis but is less easily demonstrated. There is no gradual transition zone from normal cells to burn cells as described by Leach, Peters and Rossiter, and Moritz in the moderate temperature, long duration burns. Moritz¹⁹ noted the phenomenon of demarcation on a few occasions when his animals were subjected to high temperatures for brief exposures.

Another characteristic of the flash burn is the method of healing. The burned epithelium and dermis represents a coagulative "fixed" type of necrosis, with eschar formation and subsequent sequestration, rather than the organization in the non-coagulative necrotic tissue of the moderate temperature burn. With a flash burn of average severity the epithelium grows out freely (and indeed beautifully) from normal borders and hair follicles, beneath the unorganized eschar, so that healing is rapid. Yet if the area is large and the injury deep enough to destroy the epithelium in the crypts and hair follicles, then this characteristic of demarcation will result in delayed repair from lack of epithelial islands.

The demarcation seen is probably a function of the rapid transcutaneous heat transfer. This process is most difficult to measure. It is relatively easy to compute the energy of the source, but much harder to record that delivered on the target. Physicists have told us it is practically impossible to measure the penetration of that energy into the skin. The transfer is so brief that the lag in ordinary instruments prevents recording. Yet it is felt that efforts should be continued to measure the heat penetration at various levels, for it is desirable in an understanding of the physiologic and pathologic changes created. Some of the work done on burns in the past is difficult to evaluate because of the lack of such precise physical measurements.

The studies on the effect of flash burns are being continued. This report is limited to the lesion produced in pig skin. The observations on the histo-

pathology and healing of severe trans-dermal burns are incomplete and are being extended¹³ The influence on the healing process of anemia, infection, hypoproteinemia and ionizing irradiation will be studied There is much that remains to be done Yet at present we feel that the short exposure of high intensity heat causes differences, both histologic and reparative, from those seen in moderate temperature burns Whether or not this will alter the systemic effect of the burn on the organisms remains to be seen

SUMMARY

1 Methods are described which produce a short exposure of high intensity radiant heat capable of creating a flash burn

2 Observations on the gross and histologic changes in the skin of pigs injured by flash burns indicate that the lesion is dissimilar from the ordinary moderate intensity burn

3 The healing process in flash burns is not the same as that in moderate temperature burns

4 It is felt that the differences noted are intimately related to the physical transfer of heat through the cutaneous layers

5 It is planned to extend these observations to study of the many variables which may alter not only the local changes but also the systemic effects

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DISCUSSION —DR EVERITT IDRIS EVANS, Richmond, Va The paper by Dr Pearse and his associates is timely and important The importance lies in the fact that he has developed a method which produces a flash burn which in many ways simulates the burn caused by explosion of an atomic bomb, that is, a burn caused by a vast burst of energy of very short duration but enormous intensity

The local pathologic effects on the skin appear to be different than heat of lower degree, but it remains for future study to determine how much and in what sense are altered the metabolic effects by this particular type of thermal injury

(Slide) You can see from this slide that radiation injury accounted for not much more than 15 per cent of the casualties at Hiroshima

The chief importance of Dr Pearse's presentation to this surgical group may be that he has placed in a proper light, I think, the true nature of the atomic bomb effects on civilian and military personnel

As far as recent publications and public discussions show, the chief interest, medically speaking, in the new bomb has been the radiation hazard This may be true because to most of us this hazard is bizarre and mysterious We fear most what we understand the least I would be the last to deprecate the radiation hazard imposed by this new bomb, but even superficial analysis of the lethal effects of its use at Hiroshima and Nagasaki will show that a greater number of persons died from thermal injury than from radiation injury

The surgical significance of this fact has not been stressed properly It is important because it is in the group of persons suffering from major thermal but minor radiation injury (that is, outside the two kilometer zone) that most of the salvageable will be found, if proper research and proper preparation is made for the care of these casualties

What does this proper research and proper preparation entail? This is mentioned here because, as Dr Rankin stated in his presidential address, it is mainly on the membership of this organization that the responsibility will fall for this research and development

As a nation we need at once constructive efforts which will lead to the solution of some of these problems, I state here some of the more important as I observed them at Hiroshima and Nagasaki

First, a better understanding of the pathologic physiology of the seriously burned patient as regards the shock period, renal and liver damage, and especially, in some cases of secondary burns, pulmonary complications

Second, a useful plasma substitute such as gelatin, polyoxygelation, or the new dextran, obtainable in large quantities To my mind, it is simply foolish to think that we will ever have plasma or whole blood in the necessary amounts

Third, better physical and chemical methods for the long storage of whole blood, and knowledge of the physiological effects of massive infusions of whole blood We know practically nothing of this latter matter

Fourth, practical methods for the simplest treatment of mass burn casualties, chiefly involving face and hands

Fifth, a better treatment of burns complicated by other forms of trauma

Sixth, better treatment of burns complicated by infection in states where the ordinary bone marrow response is hampered by minor radiation damage

These problems are solvable if as a group we put our shoulders to the wheel Our responsibilities as citizens and surgeons demand this Ordinarily we like to think of the atomic bomb as affecting only enemy populations It may be well for us to remember the admonition of Dr Samuel Johnson, "Think not the doom of man reversed for thee"

DR ROBERT ELMAN, St Louis, Mo Gentlemen, it seems to me that Dr Pearse's observations have an application to present problems of burns which we see in civilian life He has called attention to the fact that the kind of burn and its systemic manifestations should really be defined in terms of the kind of stimulus, that is, the temperature and duration of the thermal agent

Many years ago, in some unpublished observations, we showed that one of these systemic infections, namely, hemo-concentration, is influenced by, but not necessarily in direct proportion to, the stimulus In other words, very often we would find greater degrees of hemoconcentration with lower temperatures or with a longer duration of the thermal stimulus Indeed, we were led to the observation that quite apart from the usual three degrees of burns described in textbooks, a burn may produce three types of tissue damage

First is the simple edema without necrosis, which leads in general to loss of plasma and hemoconcentration without toxic or other systemic manifestations Second, the dry hard necrosis which leads to neither hemoconcentration nor systemic manifestation Finally, the wet necrosis, which may lead to both

Dr Pearse's photographs showed that many of these flash burns seemed to produce a thin layer of dry necrosis I would like to ask whether in any of his other observations simple edema without necrosis, or moist necrosis, was produced

DR CHARLES C LUND, Boston, Mass I want to discuss for a moment one phase of the subject that Dr Pearse took up so ably

He mentioned that the occurrence of the numerous casualties in the Boston and Hartford fires strained the available medical facilities What would it have been if it had been 200 times worse? He is absolutely right in those statements

At the Massachusetts General Hospital there were quite a large number of very competent men, well trained in the most modern treatment of burns, and that treatment was carried out very satisfactorily Over at the Boston City Hospital we had three times as many cases Our studies of burns were of much shorter duration than those at the Massachusetts General, and the small staff that had been studying burns had to spend most of its time in directing the treatment of shock and other acute problems

The doctors at the hospital made no attempt, in more than two or three cases, to carry out the complicated pressure dressing of the burns The hospital staff reverted to

the previous standard treatment of triple dye, for which the hospital had plenty of supplies and plenty of knowledge as to how to do that treatment well

When Hartford's fire came some of the patients were taken to the Hartford Hospital, which was well equipped and which cared for their patients with the most modern treatment. However, a very large number of patients were taken to a rather small hospital where there had been no particular interest in burns and where treatment was carried out by varied specialists, many of whom were not surgeons. That particular hospital had a resident staff of only two young men, and staff men did most of the work.

Someone, unfortunately, told them that Levenson and I had had published a paper on the plaster cast treatment of burns, and that the plaster cast treatment of burns was what should be done for those patients with burns of the extremities. The result was that the casts were put on by people who did not understand the physiology of that treatment, and most of the casts had to be taken off within 24 hours and other treatment given. There was real harm to some of the patients from the cast treatment.

All of this leads up to a plea for the simplest possible effective measures to be encouraged for the doctors and the population to carry out, rather than complicated methods. If it is a question between a doctor or a person carrying out an ideal method that he does not know very well, I think it is good judgment to use a slightly inferior method that he does know.

DR HERMAN E. PEARSE, Rochester, N. Y. I would like to thank Doctor Evans, Doctor Elman and Doctor Lund for their discussion. I will try to answer Doctor Elman's question. We have worked on the pig, which is very resistant to infection. The lesions produced thus far by a standard experiment of 120 Gm. of magnesium at 30 cm. distance did not become moist burns, but were covered with a dry eschar. The greater intensity deeper burns or burns produced in other animals may become moist.

In conclusion, I would like to say that I was a little hesitant about presenting this subject before this group because it is so remote from your daily lives. I decided that there was no need of being apologetic about it, for if there is ever an atomic bombing in this country, we as surgeons must take care of the casualties. If we analyze the problem and study it, at least we will be prepared.

BLOOD STASIS IN THE LUNGS AS A FACTOR IN THE ETIOLOGY OF POSTOPERATIVE PULMONARY COMPLICATIONS*

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KNOWLEDGE CONCERNING initiating factors is most important in understanding the development of pathologic states Too often the secondary or later features of the morbid process obscure the initial aberration which set the train of events in motion This applies to the pulmonary complications which follow abdominal and other operations The important rôle of blood stasis within the lungs in initiating the process which later develops into atelectasis and pneumonia has not been adequately appreciated in spite of the excellent work of Drinker⁴ Comprehension of this fact leads to a more rational approach to the prevention of these complications

It should be emphasized at this point that the etiology of postoperative pulmonary complications varies in different cases Among the causes that may be listed are retained bronchial secretion, aspiration of foreign material into the tracheobronchial tree, pulmonary embolism and primary bacterial invasion Although some of the most serious pulmonary complications may be due to the aforementioned causes, these cannot be evoked to explain the initiation of the process in the majority of cases Hypoventilation is a factor of considerable importance, but the mechanism by which its deleterious effects are produced has not been completely clarified

The importance of secretion in the bronchi in the development of pulmonary complications has been given much consideration in recent years The significance of this factor is great A logical explanation of the source of such secretions, however, has often been wanting In some cases the presence of bronchial secretions can be explained on the basis of one of the following mechanisms (1) Response to irritating anesthetic vapors or mechanical irritation of the air passages, (2) aspiration of material, such as saliva into the airway, and (3) retention of secretion caused by pre-existing pulmonary and bronchial pathology In most cases, however none of the above explanations apply An abnormal amount of fluid in the pulmonary tissues is here postulated as a frequent source of bronchial secretion There are a number of ways in which the fluid content of the lung may be increased These are (1) Circulatory stasis, (2) hypoxia, (3) cardiocirculatory failure, (4) partial obstruction of the airway, (5) general tissue changes which favor edema such as sodium retention, Vitamin C deficiency, hypoproteinemia, etc, (6) chemical and physical irritants, and (7) reduced ciliary action and lessened evaporation from the lungs associated with hypoventilation

Circulatory stasis, which is usually not mentioned in a discussion of the etiology of postoperative pulmonary complications except in cardiac patients,

is here deliberately placed at the head of the list, and is the subject considered in this paper. It is my belief that an alteration in pulmonary blood content is a factor of fundamental importance in the initiation of many postoperative pulmonary complications. Physiologists have long known that the lungs serve as a blood reservoir. The structure of the lung is well adapted to blood storage. Contrary to solid organs, such as the liver and spleen, which also act as blood reservoirs, the lungs can store a large amount of blood without any increase in external dimensions. The congested liver and spleen enlarge, whereas the congested lung may actually become smaller. The reason for the difference lies in the fact that the increased volume of blood in the lungs causes the engorged capillaries to encroach on the alveolar spaces and hence diminish the amount of gas contained in the alveoli. Diminution in vital capacity is used as an index of pulmonary vascular congestion.

Numerous studies have demonstrated the frequent alterations in blood flow and blood content which occur in various organs or parts of the body in response to physiologic demands. The magnitude of such fluctuations may be surprisingly great. Marked alterations can occur in a period of minutes. These vascular responses are due to various neurogenic, physical, chemical and hormonal factors. The relative importance of the controlling factors varies greatly from organ to organ. One must constantly bear in mind the difference between the volume of blood flow through an organ and the total blood content of that organ. The two values are not directly related. In the lungs, for example, the blood content is less when the rate and minute volume of blood flow is increased during exercise. Another very important factor, however, is the vascular status, and circulatory demands, of other parts of the body. DeBakey and associates² have referred to a "lending-borrowing" mechanism in the re-distribution of blood associated with pathologic states. In such a process the "bank" or reservoir is an important consideration. Since the lungs are one of the most important blood reservoirs in the body, the numerous factors which alter the amount of storage in the lungs deserve far greater consideration.

Hamilton and Morgan⁶ showed that a change from the upright to the recumbent position reduces the vital capacity because of a redistribution of blood. The lungs serve as a storage place for the blood which drains out of the dependent veins on lying down. This conception is substantiated by the fact that when blood pressure cuffs are applied to the four extremities while the subject is upright, and blood is trapped in the arms and legs by raising the pressure in the cuffs to a diastolic level, there is no similar reduction in vital capacity on assuming the recumbent position. But the increased blood content of the lungs during recumbency and bodily inactivity is not evenly distributed. Because of the low pressure in the pulmonary veins, gravity has a greater influence on the pulmonary than on the systemic circulation. Position plays an important role in determining the distribution of the blood within the lungs, especially during hypoventilation. The anatomical relationship of the various parts of the lung to the site of the entrance of the pulmonary veins into the left

atrium is important. A greater pressure is necessary to drain the blood from the parts of the lungs which are below the level of the veins. Moreover, the portions of the lower lobes caudad and posterior to the level of the inferior pulmonary vein are known to be the usual site of postoperative complications.

Ventilatory motion plays an important role in pulmonary circulation. The more negative intrathoracic pressure associated with inspiration causes an increase in the amount of blood entering the right side of the heart and pulmonary circulation. The left ventricle then responds by also increasing its output. A remarkable adjustment keeps the output of both ventricles essentially the same except for transient changes. Otherwise, large fluctuations in the blood content of the lungs would constantly occur. Much additional data is needed concerning the mechanism by which this adjustment is attained. Only then can it be known whether different breathing patterns with variations in the relative length of the inspiratory and expiratory phase will influence significantly the tendency toward blood stasis in the lungs. The importance of mechanical movement in aiding pulmonary blood flow has been forcibly demonstrated by Thompson's experiments⁸. In heparinized freshly killed animals alternating positive and negative intrabronchial pressure caused movement of blood through the lungs after all heart action had ceased. It is a common clinical observation that definite improvement in the peripheral circulation of patients in the early postoperative period is noted when a few deep breaths are taken. What changes in the blood content of the lung are produced by such increased ventilation have not as yet been accurately determined.

The deleterious effects of hypoventilation in surgical patients have been widely recognized. The reduced ventilation has been ascribed to splinting of respirations due to pain, respiratory depression from drugs, and bodily inactivity. Blood stasis in the dependent portions of the lungs should be added to this list. Pulmonary congestion reduces the elasticity of the lung, with resultant hypoventilation and elevation of the diaphragm.

Drinker⁵ has made extensive studies of the pulmonary changes produced in the dog by lying quietly under nembutal anesthesia for several hours. He demonstrated by means of an aerosol dye that the dependent congested parts of the lungs are very poorly ventilated. The reduced blood flow in the congested areas was proved by the distribution of intravenously injected graphite particles⁴. Drinker has also emphasized the contrast between the human being during normal sleep and the heavily sedated or postoperative patient. The respiratory amplitude and body activity are much less in the latter group. The occasional deep sigh and unconscious movements during ordinary sleep may well have a purpose.

Experimental studies have repeatedly demonstrated that infarction of the lung will not occur following embolic occlusion of a branch of the pulmonary artery unless pulmonary congestion is already present³. Since pulmonary infarction does occur in postoperative and inactive patients, circulatory stasis would appear to be present under these conditions. Also the frequent finding

of congestion in the bases of the lungs at autopsy when death occurs in the early postoperative period yields corroborative evidence. Moreover, pathologically it is often difficult to make a definite distinction between pulmonary congestion and pneumonia.

Since blood storage in the lungs is a factor in the causation of pulmonary complications, it might be expected that the incidence would be higher in those patients who normally have a larger amount of blood in their extremities, such as muscular males, which is transferred elsewhere during inactivity. The high incidence of pulmonary complications in cases of splenectomy, especially where there is marked splenomegaly, may be due to the removal of one blood reservoir which would tend to increase storage elsewhere. In general the total blood volume is not as important as the body blood distribution in influencing the blood content of the lung. The factors of primary importance are the extrapulmonary demand and the ability to empty any excess blood from the lungs.

In the day when the irritating effect of inhaled anesthetic vapors was considered the main factor in the subsequent development of pneumonia, it was anticipated that the introduction of spinal anesthesia would result in a marked reduction in the incidence of pulmonary complications. This fallacious assumption was due to misconceptions as to the initiating factors. The failure of spinal anesthesia to significantly change the incidence of postoperative pneumonia is readily understandable when it is realized that bronchial secretion may be due to blood stasis and hypoventilation.

Van Allen *et al*⁹ have demonstrated the importance of collateral respiration through the intra-alveolar pores in the maintenance of pulmonary aeration in spite of bronchiolar obstruction. Inadequate recognition has been given to this important work. Alley and Lindskog⁷ recently reported that the injection of histamine reduced or abolished collateral respiration through the intra-alveolar pores, and thought that histamine released in the operative area might be a factor in pulmonary complications. This does not seem likely, because the available evidence does not support the theory that significant amounts of histamine are released into the circulation during a properly performed operation. Moreover, pulmonary complications similar to those of the postoperative period are also seen in heavily sedated bedfast patients who have not undergone a surgical procedure.

Since bodily inactivity and depressed respirations are considered harmful factors tending to cause pneumonia, mention should be made of the Barach equalizing pressure chamber.¹ Patients may spend much time in such an apparatus in which there is relative immobility of the thorax and little movement of the rest of the body. Pneumonia has not resulted therefrom. In this chamber, however, the lungs are subjected to rhythmic pressure effects that may well affect the movement of blood in the lungs. Such patients also do not feel the usual urge to move other parts of their body, probably because of the circulatory effects of the rhythmic positive pressure to which the entire body is subjected.

The incidence of mild pulmonary complications has not been reduced in recent years as much as the frequency of the obvious postoperative pneumonia. Antibiotics and other improvements in postoperative care have lessened the frequency of clearly manifest pneumonias. Further attention should now be directed to the reduction of the milder complications by attempts to eliminate the initiating factors.

Prevention of pulmonary complications requires observance of the following:

- 1 Use anesthetic technics which do not
 - (a) depress respiration considerably
 - (b) produce even a slight degree of hypoxia
 - (c) cause labored breathing or undue resistance in the airway
 - (d) depress systemic circulation and thus favor blood storage in lungs
- 2 Remove secretions early in the tracheobronchial tree
- 3 Provide for good ventilation of all parts of lungs in the postoperative period
- 4 Reduce pulmonary blood stasis by maintaining good blood flow in other parts of body
- 5 Minimize pain that interferes with good pulmonary ventilation
- 6 Obtain aid of gravity in draining parts of lung below the level of the pulmonary veins by turning patient periodically completely on the side or to a prone position
- 7 Avoid hypotension because of unfavorable effect on blood distribution in the body
- 8 Avoid abnormal increases in blood volume

CONCLUSIONS

The muscular inactivity and depressed function of the surgical patient during and immediately after operation lessens the demand for blood in large portions of the body. A resultant accumulation of blood occurs therefore in some viscera. The lungs are an important blood reservoir. Because of the low pressure in the pulmonary venous system, position will play a significant role in determining the distribution of the blood accumulated in the lungs. Abnormal ventilatory motion and little change in body position over a period of some hours also play a role.

The blood stasis in the dependent part of the lungs is a factor which predisposes the postoperative patient to the development of atelectasis and pneumonia. More attention should be directed to the avoidance of pulmonary blood stasis since this is an important *initiating* factor. The lower incidence of postoperative pneumonia since the advent of chemotherapy does not mean that the process is primarily an infectious one in most instances. Prophylaxis of postoperative pneumonia depends largely on eliminating the factors that render the surgical patient more prone to a secondary bacterial invasion. Thus the undesirable sequence of events may be checked at its onset.

The author is keenly aware of the present lack of direct measurements of the blood content of the lungs in various physiologic and pathologic states. More investigation of circulatory alterations within the lungs of surgical patients is needed. In the future anesthetic technics should also be evaluated on the basis of their effect on the blood content in the lungs. Pulmonary blood stasis should be included in the list of etiologic factors in postoperative pulmonary complications. Although this paper has dealt with surgical cases, similar mechanisms are also present in the inactive, bedfast medical patient.

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FIG 1

Comparison of Methods

General Principle

Lumen

Transverse cut



Fish-mouth cut



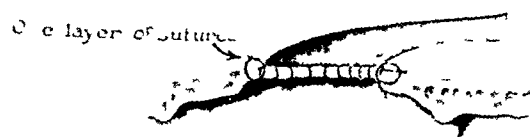
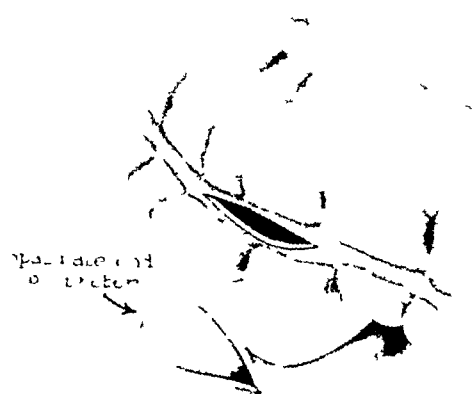
Oblique cut



Spatulate
Opening



Ureterocolic Anastomosis



Direct Anastomosis



Direct Elliptical Connection

FIG 2

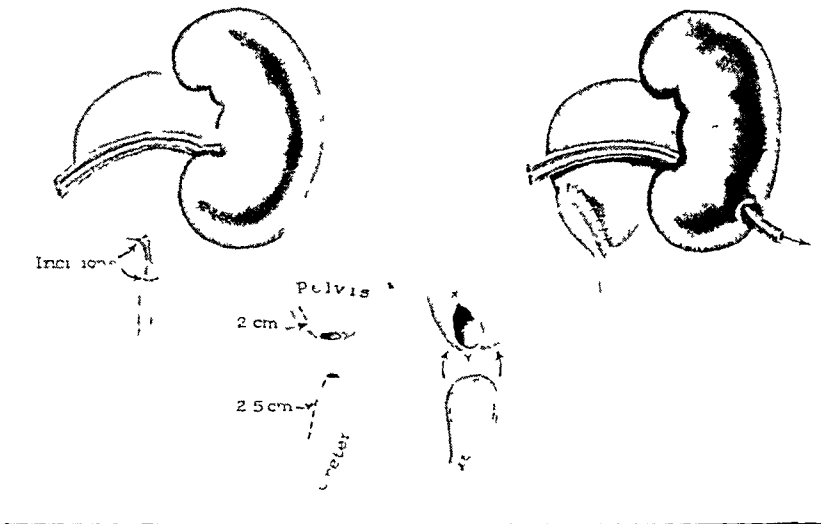
FIG 1—Comparative diameters of terminal ureter prepared by various technics
FIG 2—Anastomosis of ureter to colon by direct elliptical anastomosis provides maximum diameter of stoma

to difficulty in obtaining close opposition with skin or mucous membrane in making an anastomosis

The principle of elliptical connection which is made possible by a single slit at the terminal end of the ureter or urethra appears to overcome the tendency to constriction in the lumen. When the tube is slit in this manner, its terminal portion becomes spatulate in shape with a diameter π times the diameter of the original tube. Furthermore, when the spatulate end is utilized in making a direct anastomosis to the skin or to another viscus, the actual caliber of the smaller tube is in no way jeopardized by healing of the anastomosis, since only one stitch directly involves its circumference. When this technic is employed,

FIG 3

Hydronephrosis
(without excision of pelvis)



Hydronephrosis
(with excision of pelvis)

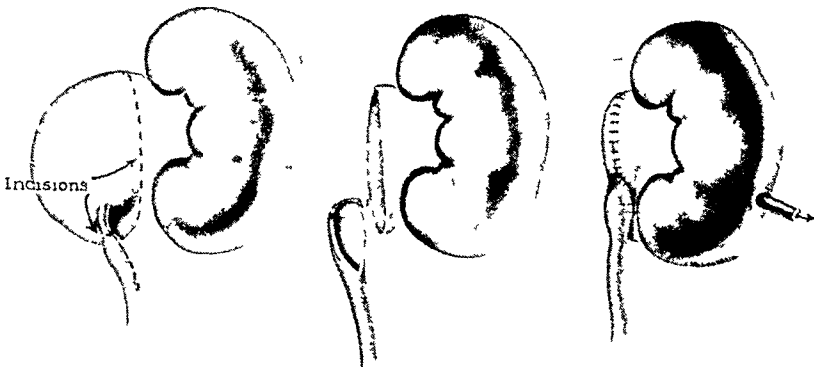


FIG 4

FIG 3—Principle of elliptical anastomosis applied to correction of congenital hydronephrosis

FIG 4—When pelvis is large the redundant portion is excised and elliptical connection with upper ureter carried out

any tendency to constriction at the point of epithelial union will involve only the large circumference of the stoma and will not, in so doing, cause a decrease in caliber of the tubes that are connected by the anastomosis

We first applied this principle of anastomosis in performing ureterosigmoidal transplantation (Fig 2), hoping to eliminate some of the disadvantages inherent in previous transplant operations. Most of the earlier technics employed the tunnel principle in the belief that such an arrangement provided a valve to protect the upper urinary tract from reflux. Whether a valve mechanism actually operates effectively in this circumstance has never been deter-

Reimplantation of Ureter into Bladder

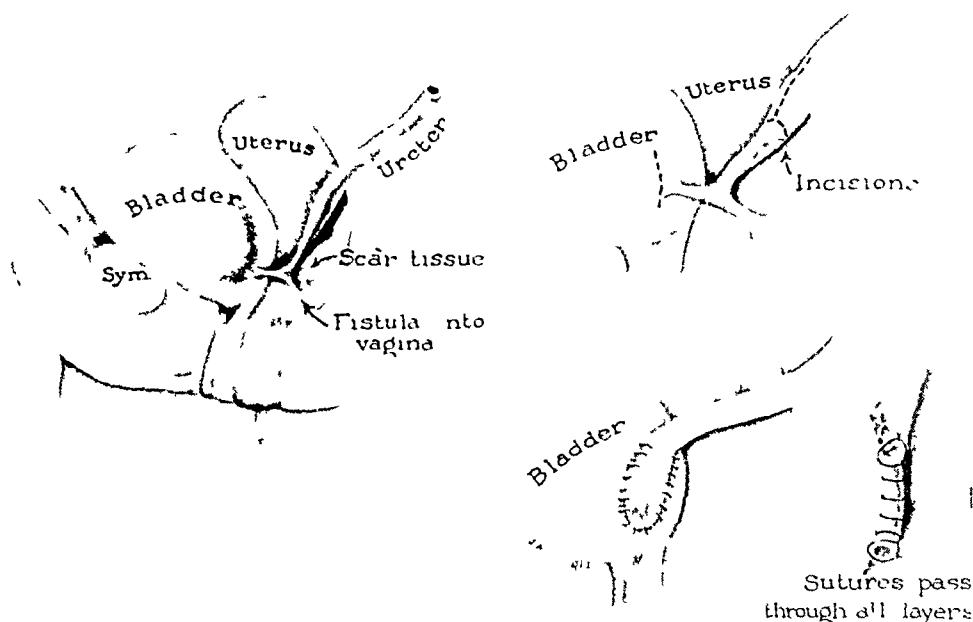


FIG 5—Reimplantation of ureter into bladder by elliptical anastomosis

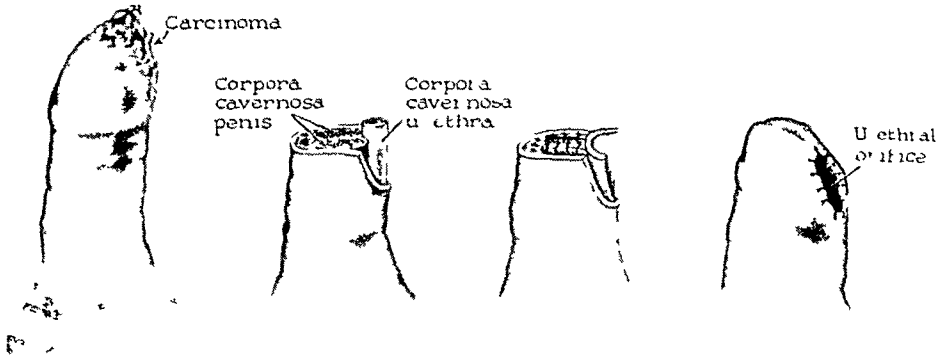
mined. Many investigators have held the view that reflux is prevented by unimpeded peristalsis in a normally functioning ureter, and that the natural oblique insertion of the ureter into the bladder is a fortuitous arrangement rather than a protective one.

The tunneling operations of uretero-intestinal anastomosis are often complicated by postoperative hydronephrosis due to stricture at the site of anastomosis, and there are three frequent sites of obstruction: concentric constriction of the terminal ureter that projects into the lumen of the bowel, fibrosis in the tunneled area, and peritoneal constriction at the point where the ureter enters the site of anastomosis.

Ureterosigmoidal anastomosis by direct elliptical connection avoids all of these points of constriction, and has demonstrated its value in the uniform avoidance of ureteral and renal dilatation in laboratory animals and in over 20 patients that have been operated upon during the past year at the University

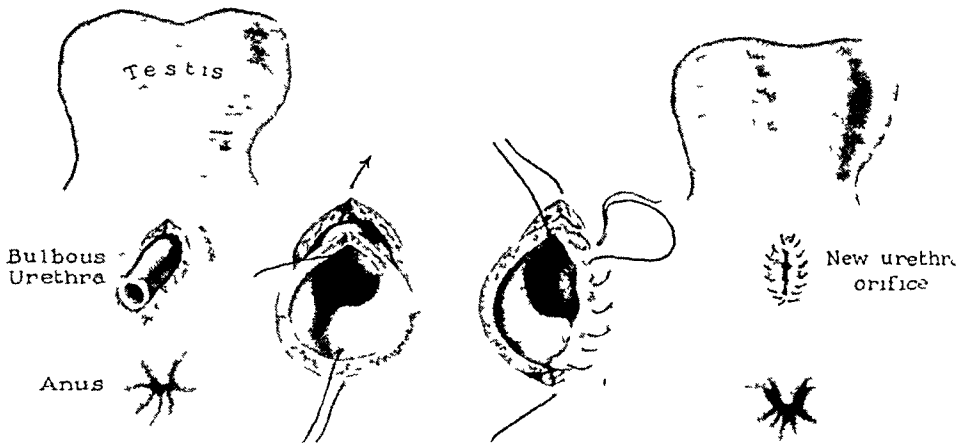
Urethra with Partial Amputation of Penis

FIG 6



Urethra with Radical Amputation of Penis

FIG 7



Vaso-epididymal Anastomosis

FIG 8



(Legends on opposite page)

of Michigan Hospital. Another advantage of this technic has been demonstrated in the successful transplantation of grossly dilated ureters in four of our patients; two of the latter had far advanced bilateral hydro-ureters and hydronephrosis. Personal communications from many surgeons who have performed this operation since the preliminary report of the procedure in May, 1948, have revealed that it has been successful in nearly a hundred cases at the present time.

The principle of elliptical connection has also been applied successfully in reimplanting the upper end of the ureter for the treatment of congenital hydronephrosis. When there is a relatively small renal pelvis (Fig. 3) the ureter is severed and a terminal slit is made on one side for a distance of about 1 cm., then a vertical incision of equal length is made at a dependent point in the renal pelvis and direct anastomosis is made. When a large and redundant pelvis is encountered (Fig. 4) it is excised and anastomosis of the spatulate upper ureter is made at the lower end of the incision in the pelvis. We have not employed a splint at the site of anastomosis but have directed the urine by nephrostomy for two weeks.

This same technic of anastomosis has been employed successfully in three cases for the reimplantation of the lower ureter into the bladder. In the case illustrated by the artist's sketches (Fig. 5) there was a ureterovaginal fistula, and the ureter and renal pelvis were moderately dilated. The operative approach was made above the site of previous operation, and the ureter was picked up retroperitoneally and followed downward to the area of cicatrix, where it was cut across and a slit was made at a favorable site on its inferior aspect and direct anastomosis was made between the two viscera by interrupted catgut sutures, the stitches passing through all coats of both structures. Diversion of the urine was effected for two weeks by means of a T-tube placed in the ureter above the site of anastomosis. Six weeks after operation excretory pyelograms showed that the ureter and kidney had returned to normal size. A cystogram was made after the bladder had been filled with sodium iodide solution to a point of painful distention, yet there was no reflux of the contrast medium that could be seen on the roentgenograms that were made under these conditions.

Elliptical anastomosis has been employed advantageously in connection with the performance of cutaneous ureterostomy in two cases, and these comprise the sole instances in our experience where stricture at the mucocutaneous junction has been avoided.

Four patients with cancer of the penis have had amputations in which elliptical anastomosis of the urethra to the skin has been employed. In two cases a local amputation was performed (Fig. 6) and the method was found to

FIG. 6—Following partial amputation of penis, this method provides a satisfactory meatus.

FIG. 7—Perineal urethrostomy by elliptical anastomosis prevents stricture.

FIG. 8—Anastomosis of vas deferens to epididymis is simplified by using elliptical connection.

simplify the technic of operation Follow-up examination of both patients demonstrated the new meatus to be free from stricture

The bugbear of stricture in perineal urethrostomy following radical amputation of the penis is notorious, and has been a serious complication of the operation In two patients who had radical amputation the bulbous urethra was anastomosed to the perineal skin (Fig 7) by direct elliptical connection, and strictures have been avoided in both instances

Another situation in which the principle was successfully employed involved the anastomosis (Fig 8) of the vas deferens to the epididymis in treating sterility due to a congenital stenosis in the duct of the epididymis The patient had been shown by testicular biopsy to have normal spermatogenesis, yet his semen contained no spermatozoa A slit 1 cm long was made in the globus major of the epididymis and fluid obtained from it was found to be made up of active sperms Elliptical anastomosis between the slit terminal vas deferens and the incised epididymis was easily effected, and six months after operation the patient had a semen which contained spermatozoa in normal number and having normal activity

The principle of elliptical anastomosis is manifestly not a new concept, because the technic has previously been utilized in all fields of surgery But the distinct advantages of the method in the field of urologic surgery apparently have never before been asserted The clinical value of elliptical anastomosis is demonstrated by the various operations that have been described in the present communication

DISCUSSION —DR ROBERT LEE PAYNE, Norfolk, Va I am intensely interested in Doctor Nesbit's paper for several reasons It will be patent in my discussion Whenever a ureter is divided, stricture inevitably and always results unless there is a mucosal anastomosis made immediately after the division of the ureter That is why Simon in 1869 first recommended a nephrectomy for ureteral fistula and this was followed by attempts of anastomosing the ureter in the bowel, the skin, the bladder and the vagina The principal objection to all methods of anastomosis has been a development of stenosis, and, second, the possible danger of ascending infection from regurgitation With the flush anastomosis to the bladder wall, stricture is most liable to result

In 1908, in a monograph on this subject, I stated in my article that I did not believe regurgitation took place, or at least did not account for ascending infection In none of my cases have I ever seen infection, present at the time of operation, fail to clear up after the split double flap type of anastomosis, and I stated I did not believe there is a normal ureteral valve at the ureteral orifice to prevent regurgitation Pozzie, Modkinsky and Desnos report leakage of urine from the bladder through the vesical stump of a divided ureter and Hartman reports leakage from the vesical stump following a nephrectomy

Since in all of my cases of ureteral fistulae infection has cleared up rapidly following the double flap method of anastomosis, I am led to believe that regurgitation plays a small role, if any, in ascending infection following ureterovesical implantation My idea is that the bladder wall contracts around the double flap type of anastomosis and possibly prevents regurgitation The musculature of the bladder is composed of an inner and outer longitudinal layer and a middle circular layer If the flap anastomosis is made at the summit of the bladder and the ureter thus passed through the entire bladder wall, hence through this mesh-like arrangement of muscle fibers, it seems reasonable to believe that

vesical contraction would produce a valve-like constriction of the ureter and thus prevent any forcible regurgitation

In 1903 Van Hook recommended splitting the ureter on one side, as Doctor Nesbit advises thus making an elliptical flare, and in these cases the ureter was anastomosed flush to the bladder and this resulted in stricture. By my method of anastomosis the ureter is split on both sides and these lateral flaps are then drawn into the bladder by traction sutures and fixed. Regarding the fixation of the flaps, I recommended that a layer of mucous membranes on either side of the vesical incision be removed, thus securing for the flaps an approximation of connective tissue to connective tissue. Two cases of this flap-type of anastomosis were reported by me, with illustrations, in the Journal of the American Medical Association, October 17, 1908, Page 1321. One of these cases had the left kidney lowered to accommodate for a shortened ureter.

Bovee successfully lowered the kidney for a shortened ureter in dogs, but my case reported 1908 was the first time this was done and reported in the human.

Over a period of nearly 43 years I have never had the opportunity to do this operation but 12 times. In one of my patients the surgeon had operated and tied both ureters, and the individual had been totally anuric for exactly six days before the diagnosis was made. I remember Doctor Starr Judd telling me that he had seen an individual with both ureters ligated, who had been totally anuric for nine days. In my patient just referred to, who had been totally anuric for six days, one of the ureters functioned normally through the bladder after the ligature had been removed, but the other ureter developed a ureteral fistula after removing the ligature and this ureter 12 weeks later was implanted into the bladder by the split double flap method shown to you in the slides on the screen.

This flap method of anastomosis has been successfully used by me, not only in uniting the ureter to the bladder, in resections of strictured areas at the uretero-pelvic junction in the kidney, but also in planting the ureters into the bowel.

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THE PATHOGENESIS OF HYPERTHYROIDISM*

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INTRODUCTION

HYPERTHYROIDISM results from the release of an excess of the hormone normally produced by the acinar cells of the thyroid gland. Such an excess of secretion may be produced by a localized group of cells within the thyroid gland, a so-called adenoma, or it may be due to a generalized overaction of the cells of the thyroid gland. The latter results from increased production of the thyrotropic hormone. Evidence will be advanced to show that the increased production of this thyrotropic hormone which is secreted by the glandular hypophysis results in turn from an increased secretion of the neural hypophysis, the latter being under nervous control from the supraoptic and the paraventricular hypothalamic nuclei. The hypothalamus, including these two nuclei and the centers of the sympathetic and the parasympathetic systems as well, is subject to excitation and suppression from the central nervous system, and as a consequence of the exteroceptive and interoceptive impulses which reach the latter, the neural hypophysis may be influenced. It must be inferred that different subjects differ constitutionally with respect to the degree to which this chain of events activates the hypophysis, the action as such may be considered a normal one for the regulation of visceral functions. Evidence to support these statements will be presented from experimental and clinical data.

EXPERIMENTAL DATA

Source of thyrotropic hormone In previous reports (Heinbecker,^{1,12} 1944, 1946) it was shown that following denervation of the neural hypophysis in the dog (Fig 1), either by section above the median eminence (puncture, Type 1) or by a transverse section caudal to the stalk in front of the mammillary bodies (puncture, Type 2) there occurs a change in the cytology of the glandular hypophysis which is characterized by a marked loss of basophile cells and an increase in eosinophiles (Fig 2). If animals so operated on are compared with animals simply or totally (median eminence included) hypophysectomized, it is found that in both atrophy of the thyroid gland occurs (Fig 3). This indicates that the atrophy of the thyroid gland is brought about by loss of the basophile cells, because the puncture type dog has an adequate number of active eosinophiles left. Their activity is evidenced by a decrease in circulating lymphocytes and by a decrease in insulin sensitivity. In females there occurs also a loss of ovarian follicles, and in males a failure of maturation of

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† Recipient of a grant-in-aid of research from the Commonwealth Fund and the United States Public Health Service

the spermatocytes. In these puncture dogs the adrenal glands and the interstitial tissues of the ovary and of the testis remained normal. On the basis of such evidence it is concluded that the basophile cells of the glandular hypophysis are the source of hormones trophic to the thyroid gland, to the ovarian follicles, and to the tubule cells of the testis. From these experiments it may be concluded also that decreased activity of the supraoptic and the paraventricular

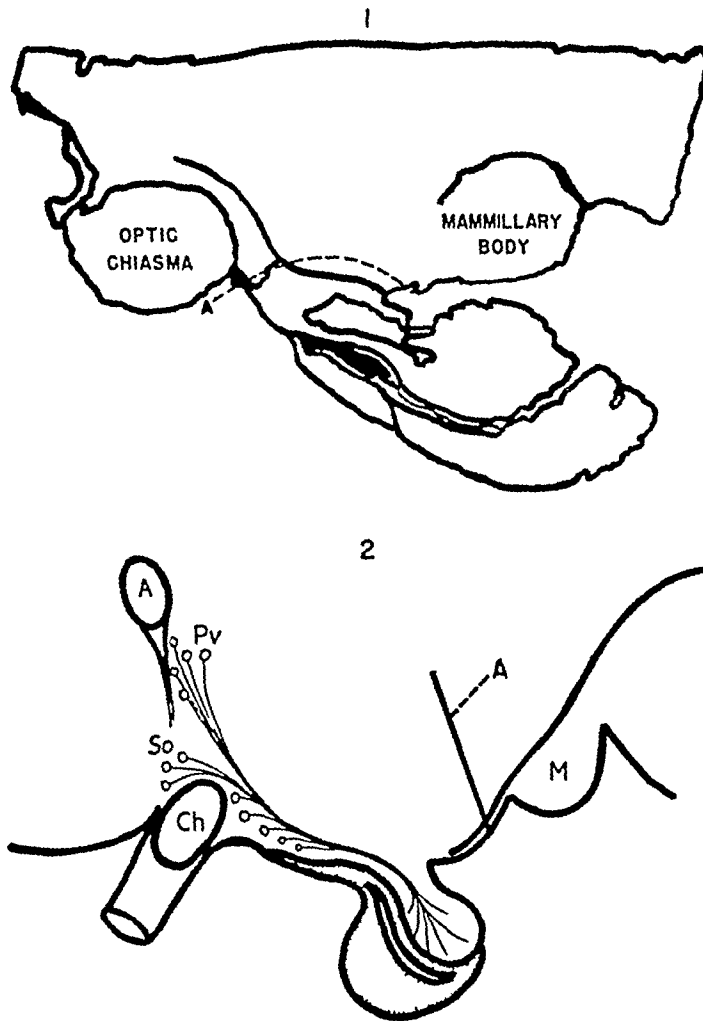


FIG 1—Diagram to indicate operations to denervate the neural hypophysis

1 Complete denervation called Puncture Type 1, performed through the oral approach

2 Partial denervation, Puncture Type 2, by severance of afferent fibers from the caudal and superior areas to the paraventricular and supraoptic nuclei, performed through the temporal approach

of the hypothalamus is responsible for the loss of hypophysial basophile cells noted following puncture operations. The decreased activity of these nuclei reduces the formation of posterior lobe hormone, and thus is responsible for the loss of basophile cells in the glandular hypophysis. Other influences which modify basophile cell maturation will be considered later in this presentation.

EFFECT OF EXOGENOUS POSTERIOR PITUITARY HORMONE ADMINISTRATION
ON THE CYTOLOGY OF THE GLANDULAR HYPOPHYSIS

Exogenous whole posterior lobe hormone was administered to two female and one male dog for periods varying from 28 to 45 days. During the period of hormone administration the dogs were kept in metabolism cages and fed a mixture of dog biscuits and horse meat. Daily urine collections were made. Periodically blood cholesterol and blood sugar determinations were run. On two of the dogs frequent total and differential blood counts were made before and during the period of hormone administration.

The dogs remained in good general health, their urine output was slightly but not significantly decreased, their appetite remained good. In two of the dogs given 45 and 90 units respectively of posterior lobe hormone for a period of 60 days, the blood circulating lymphocytes gradually increased to 30 per cent above the control values obtained before the period of hormone administration began. There was first an increase in blood cholesterol of 15 per cent with a later decrease to a little below the preinjection level.

TABLE I—*Cell Counts of Two Dogs Given 45 Units Posterior Pituitary Hormone, Dog 1 for 28 Days and Dog 2 for 45 Days*

Dog 1			
	Eos	Baso	Chromo
	58.6%	14.6%	26.8%
Dog 2			
	51.9%	17.2%	30.9%
Average normal controls			
	38.5%	9.2%	52.3%

At the end of the period of observation the dogs were sacrificed and complete autopsies performed. The pituitary glands were fixed in 10 per cent formalin, serially sectioned at 5 microns, and differentially stained according to the method of A. T. Rasmussen. The thyroid gland, the gonads, and other endocrine organs were studied in detail. The percentage of basophile cells was increased in the glandular hypophysis as a result of posterior lobe hormone administration (Table I). The thyroid gland showed actively secreting cells (Fig. 3). The ovaries showed an increase in the thickness of the germinal layer due to many large growing follicles. The testes showed active spermatogenesis.

Since the major result of excess posterior lobe hormone on the glandular hypophysis of the normal animal is an increase of basophiles and a decrease in their number follows a decrease in the amount of posterior lobe hormone, it is concluded that the basophiles are normally regulated in number and in the amount of their secretion by the activity of the neural hypophysis.

EFFECT OF THYROIDECTOMY, CASTRATION AND HYPERTHYROIDISM
ON THE GLANDULAR HYPOPHYSIS

It has been shown in this laboratory and by others (Severinghaus, 1935² and Zeckwer *et al.*, 1935³) that removal of the thyroid gland or of the gonads

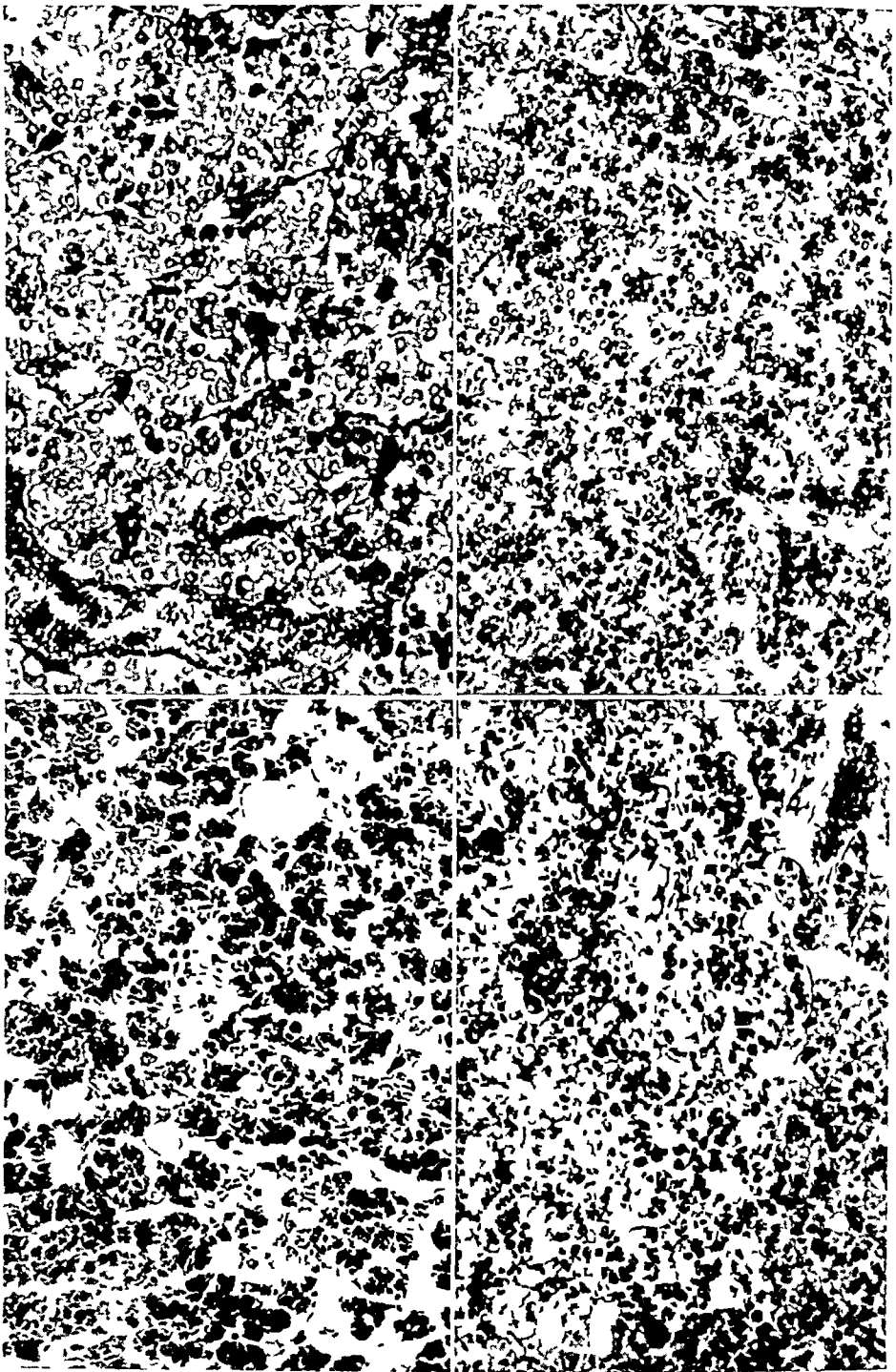
or of both together results in a marked increase in the hypophyseal basophile cells. Such basophiles may become degranulated and filled with clear material. The interpretation made is that removal of the thyroid, or the gonads, or of both together, permits an increase of hypophyseal basophile cells, which in time become altered cytologically because of an accumulation of secretory products. These are not released or, if released, are ineffective, because of a lack of thyroid, of follicular, or of seminiferous tubule hormone. The same condition results eventually after denervation of the neural hypophysis. Up to two years after such an operation the effect is a loss of hypophyseal basophiles, with resultant depression of thyroid and gonad function leading to eventual atrophy of the thyroid, of the ovarian follicles, and failure of maturation of the spermatocytes. Eventually, such atrophic changes will be reflected in the cytology of the glandular hypophysis by an increase in basophile cells (unpublished data in this laboratory). The hormones of the altered basophile cells are unable to restore to a normal state the atrophic glands to which they are trophic normally.

TABLE II—*Effect of Desiccated Pork Thyroid 0.1 Gm per Kg Per Day for 42 Days on the Cytology of Glandular Hypophysis of the Dog*

Dog No.	Eos	Baso	Chromo
Dog X13			
	44 1%	6 6%	49 3%
Dog X36			
	10 3%	3 3%	56 4%
Average normal controls			
	38 5%	9 2%	52 3%

In other experiments it was found that the administration to two dogs of thyroid gland substance (0.1 Gm per Kg body weight per day for 42 days) did not increase, but rather tended to decrease the basophile cells of the hypophysis (Table II). The eosinophile cells showed a slight increase. Severinghaus, Smelson and Clarke² (1934) on the other hand, found in thyroid-fed rats an increase in basophiles cytologically indistinguishable from that found following castration or thyroidectomy. The hyperthyroid rats showed a pronounced increased acidophilia. The acidophile changes were in direct contrast to those seen after thyroidectomy in the rat in which the acidophiles revert entirely to chromophobes, or after castration, where they decrease in size and number. Apparently the response of the glandular hypophysis to exogenous thyroid substance varies with the animal species, with the amount, and with the duration of thyroid administered (Romeis,⁴ 1940).

Our experience with the cytology of the glandular hypophysis of man, with hyperthyroidism, has been limited due to lack of available material. In a typical case of a man of 51 years who died without therapy in thyroid crisis after 20 years of hyperthyroidism due to diffuse overaction of the thyroid acinar tissue (BMR +67 per cent) there is shown a marked increase in basophile cells, and a decrease in eosinophile cells (Fig. 4).



C

D

FIG 2—A Photomicrograph $\times 95$ of glandular hypophysis of normal dog showing eosinophiles 39.8 per cent, basophiles 9.4 per cent, chromophobes 50.8 per cent

B Photomicrograph $\times 95$ of glandular hypophysis of puncture dog Type 1 showing eosinophiles 64.2 per cent, basophiles 0.0 per cent, chromophobes 35.8 per cent two years following puncture operation

C Photomicrograph $\times 95$ of glandular hypophysis of puncture dog Type 2, one year after operation showing eosinophiles 52.5 per cent, basophiles 1.5 per cent, chromophobes 46 per cent

D Photomicrograph $\times 95$ of glandular hypophysis of normal dog given 25 units posterior lobe hormone for 28 days showing eosinophiles 51.9 per cent, basophiles 17.2 per cent, chromophobes 30.9 per cent

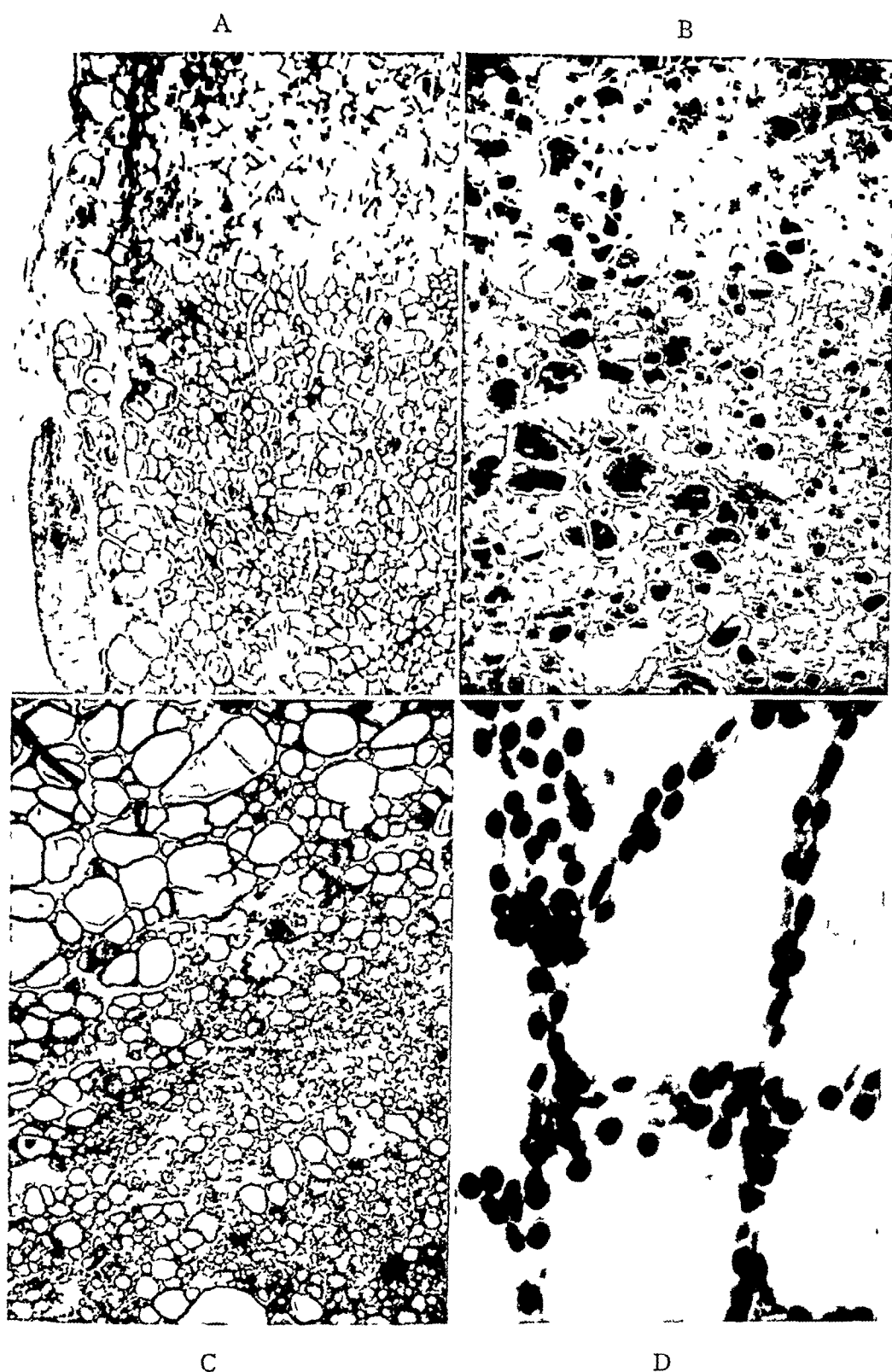


FIG 3—A Photomicrograph of thyroid gland of normal dog
B Photomicrograph of thyroid gland of totally hypophysectomized dog
C Photomicrograph of thyroid gland of puncture dog Type I
D Photomicrograph x475 of the thyroid gland of normal dog after 28 days of posterior lobe extract. Note atrophic state of thyroid gland of B and C on comparison with A. Note active acinar tissue in D.

EFFECT OF HYPOTHALAMIC PUNCTURE AND OF TOTAL HYPOPHYSECTOMY
ON THE PARATHYROID GLANDS

Material and data were obtained on four Type I puncture dogs and four totally hypophysectomized dogs. They were sacrificed two or more years following their operation. Autopsy studies revealed that in the Type I puncture dogs, and in totally hypophysectomized dogs, the parathyroid glands became enlarged to four to six times their average normal size for dogs of similar size and age. Marked parathyroid enlargement also was found in two totally hypophysectomized and thyroidectomized dogs sacrificed two years after the

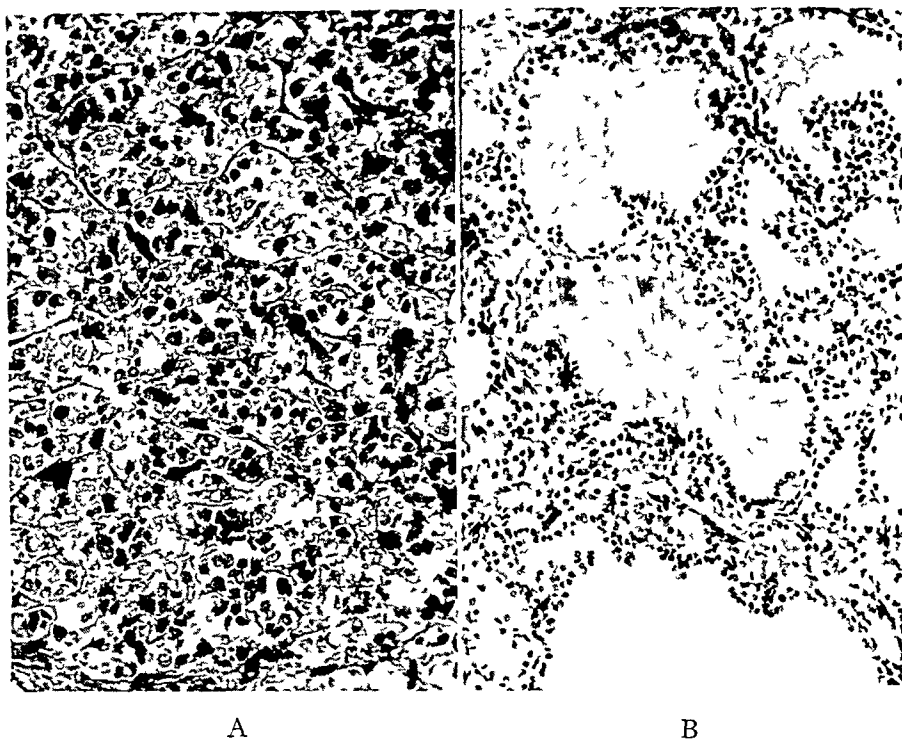


FIG 4—A Photomicrograph $\times 90$ of human glandular hypophysis from patient with marked hyperthyroidism showing basophile cell preponderance. B Photomicrograph $\times 90$ of thyroid gland of patient C, Figure 7, showing actively secreting acinar tissue.

removal of the hypophysis and the thyroid glands. On the basis of this evidence, it is concluded that the basophilic cells are inhibitory to the parathyroid glands. The microscopic examination of such enlarged parathyroid glands (Fig 5) reveals that the enlargement is due to an increase in normal appearing closely packed cells. Because of this it is concluded that they are functionally active. Still, in the dogs with such enlarged parathyroid glands the serum calcium and serum phosphorus values remained within normal limits and no demineralization of the bones occurred.

One Type I puncture dog with enlarged parathyroid glands (Fig 5) was sacrificed seven and one-half years after the original operation. Hypophysial basophilic cells essentially absent up to two years after such an operation had

returned, and their number was greatly increased, being 40 per cent of the differential count as compared with a normal of nine to ten per cent. It is significant to note that the basophile cells are degranulated and filled with clear material considered by us to represent a retained secretory product. Because

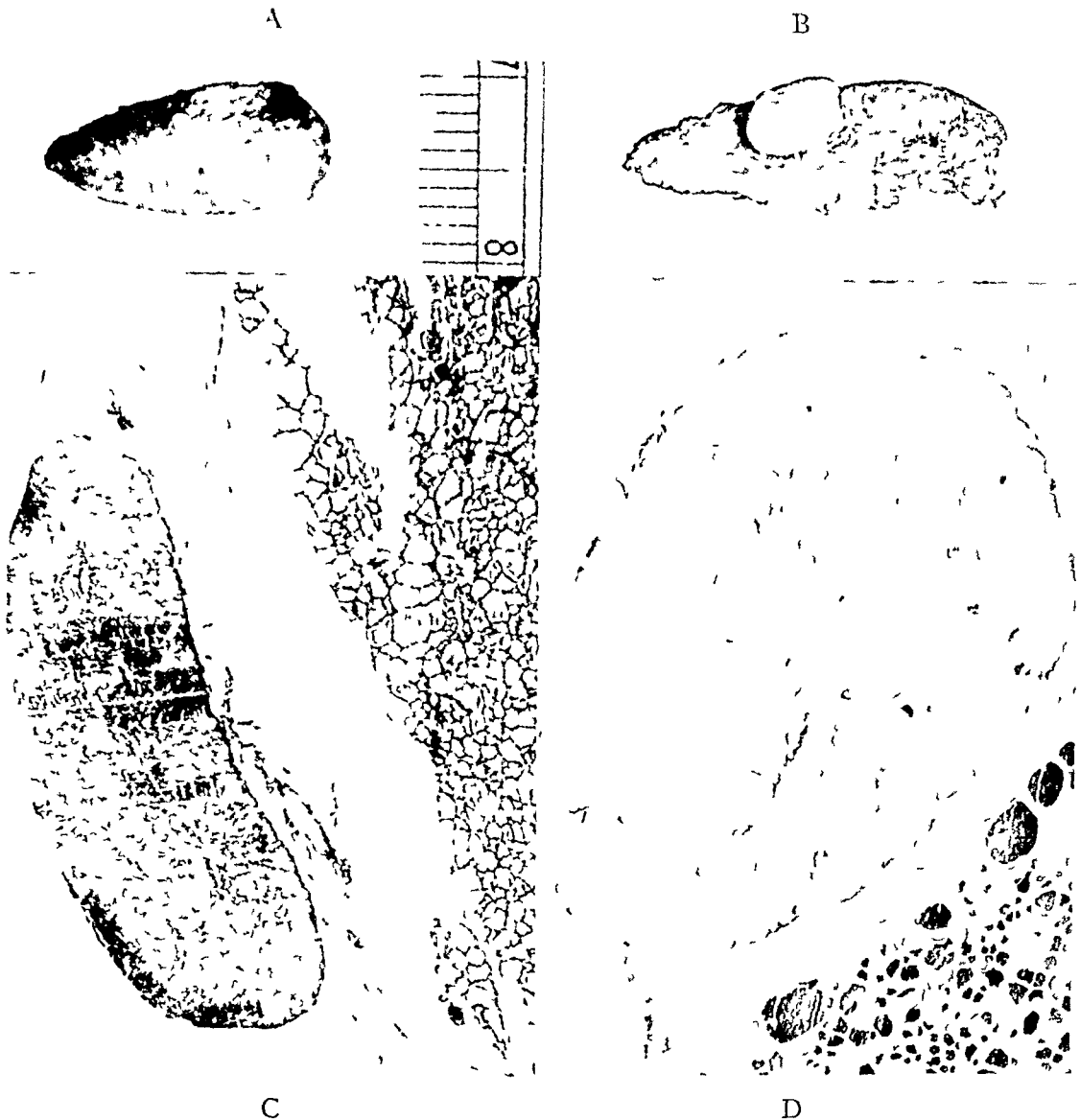


FIG 5—A Photograph of parathyroid gland of normal dog
B Photograph, same magnification as in A of thyroid gland of puncture dog Type I, seven and one-half years after operation, showing marked increase in size of parathyroid gland
C Photomicrograph $\times 12$ of largest normal parathyroid gland encountered
D Photomicrograph $\times 12$ of parathyroid gland of totally hypophysectomized dog two years after operation. Note the gland is composed entirely of parathyroid cells

of the persistent atrophic state of the thyroid gland and the ovaries, however, it is inferred that the secretion had not been released or was not effective

EXOPHTHALMOS

Experimental data Loeb and Friedman⁵ (1931) and Marine and Rosen⁶ (1933) produced exophthalmos by the administration of whole pituitary and

of thyrotropic hormone in thyroidectomized guinea pigs Dobyns⁷ (1946) produced exophthalmos in the guinea pig by the administration of thyrotropic hormone to both normal and thyroidectomized animals His studies of the orbital tissues showed edema and early fatty infiltration into the muscles From such studies it is evident that thyrotropic hormone alone can cause exophthalmos in some animals The effect disappears with the cessation of

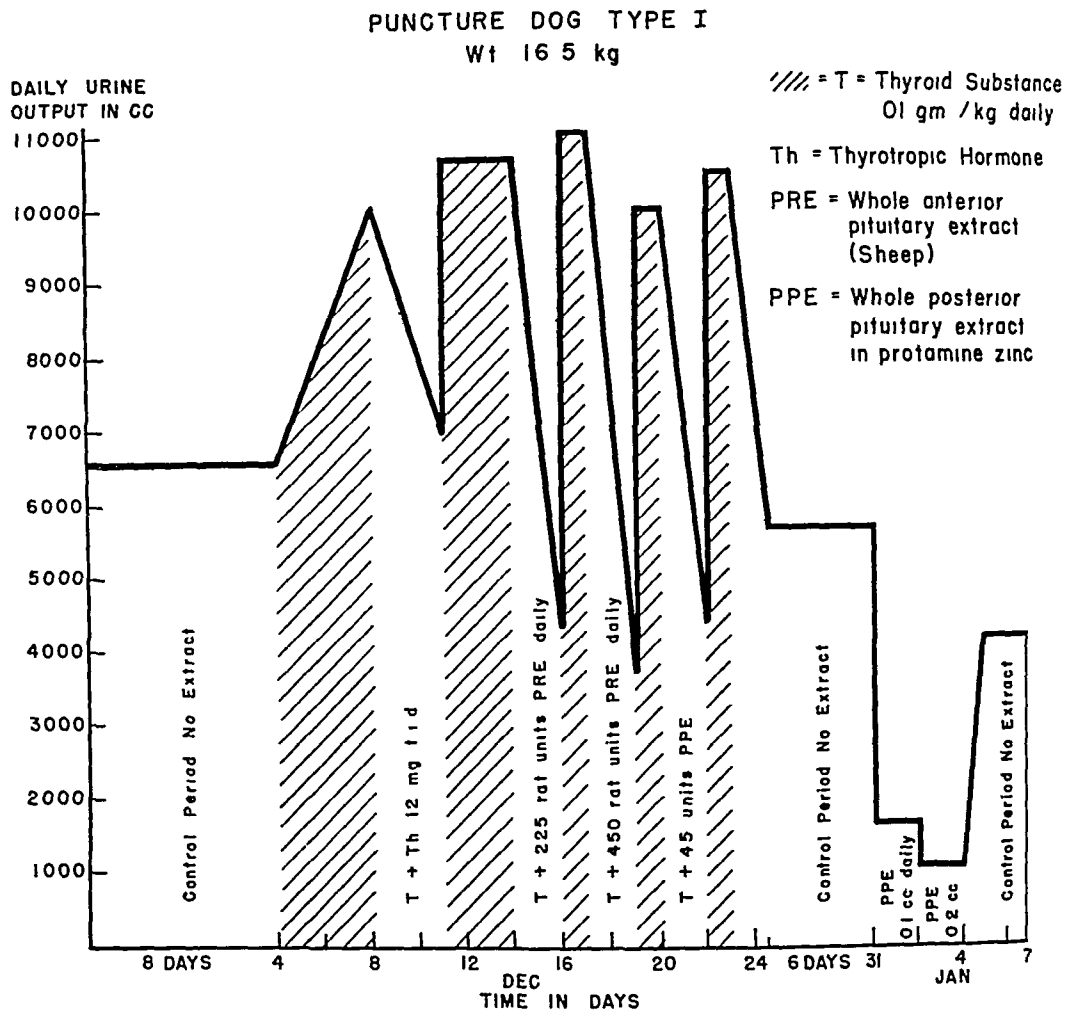


FIG 6—Chart to show diuretic effect of thyroid substance in a diabetes insipidus dog due to Puncture Type I It shows also the antidiuretic effect of purified thyrotropic hormone, of whole anterior pituitary extract, and of whole posterior pituitary extract in protamine zinc

hormone administration Significantly the injection of pituitary extracts in animals produces both in the eye muscles and in skeletal muscles changes that closely resemble those found in corresponding muscles in man suffering from Graves' disease The orbital tissues appear to be more susceptible to the water retaining influences of the hormones, although skeletal muscles may be similarly but less severely affected

In this laboratory, studies pertinent to the problem of exophthalmos were made on three dogs Two were totally hypophysectomized, and in one the

neural hypophysis was denervated. As a result of the operations all three dogs exhibited marked diabetes insipidus. The two totally hypophysectomized dogs were given daily administration of thyroid gland powder, 0.1 Gm per Kg throughout the experimental period. In addition, they were given at stated intervals, doca, whole adrenal cortical extract, anterior pituitary extract (preloban), purified thyrotropic hormone and posterior lobe hormone. The dosages used in the dog with the neural hypophysis denervated, and the results obtained, are shown in Figure 6.

From the results of the experiments it can be stated that preloban, thyrotropic hormone and posterior lobe hormone are markedly antidiuretic. They, therefore, would tend to retain water in the tissues. This finding is offered as the mechanism through which they produce exophthalmos in animals and in man.

Thyroid extract has been shown to be markedly diuretic in the hypophysectomized and the puncture type dog. It would, therefore, tend to compensate for the water retaining influence of the thyrotropic hormone itself. Of similar import is the observation that removal of the thyroid gland in dogs stops the temporary diabetes insipidus which follows simple hypophysectomy (Mahoney and Sheehan,⁵ 1935). This observation was confirmed in this laboratory. It follows that exophthalmos might well become augmented by a reduction in circulating thyroid hormone below its normal level.

In two other dogs chronic adrenal deficiency was produced by bilateral adrenalectomy. The dogs were maintained in good condition by the implantation of pellets of desoxycorticosterone, one for a period of nine months, the other for 14 months. At autopsy a generalized increase in lymphoid tissue was noted. Complete and differential white blood counts made periodically revealed a gradual increase in the number of circulating lymphocytes. Thus in one dog four months after operation the blood picture was as follows:

RBC	WBC	EOS	BASO	STABS	SEGS	LYM	MONO
5.17	15,875	13.5%	0%	0.5%	43%	42%	1%

One year after operation the counts were:

6.96	14,600	5.0%	0.5%	8%	24.3%	67.8%	1.7%
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Average normal control counts for dogs in this laboratory were:

7.1	12,500	5.2%	0%	1.1%	62.1%	28.6%	3.0%
	±5000						

In other experiments it was shown that in the dog the administration of thyroid powder 0.1 Gm per Kg tends to lower rather than raise the number of circulating lymphocytes. A similar effect was obtained by the administration of purified thyrotropic hormone. For these reasons the increase in circulating lymphocytes which characterizes Graves' disease are taken to indicate hypofunction of the eosinophile-adrenal hormone complex rather than hyperfunction.

of the basophile-thyroid hormone complex, because the latter would decrease rather than increase the circulating lymphocytes

Illustrative Case A 45-year-old colored male was admitted to Barnes Hospital January 10, 1947, because of a bulging of the right eye and diplopia. Investigation revealed an indefinite enlargement of his thyroid gland, BMR +26. His blood cholesterol was 185 mg per 100 cc, and WBC was 9000, with circulating lymphocytes 34 per cent. After study he was discharged for clinic treatment with propyl thiouracil 50 mg, tid. He was readmitted to the hospital September 15, 1947, with bilateral malignant exophthalmos and keratitis (Fig 7). His BMR now was -26, his blood cholesterol 277 mg per 100 cc. A bilateral maxillary sinusotomy and ethmoidectomy was performed to save his sight.

The case illustrates two well known facts: (1) that exophthalmos frequently is associated with hyperthyroidism and (2) that exophthalmos frequently becomes more marked with the lowering of basal metabolism by treatment.

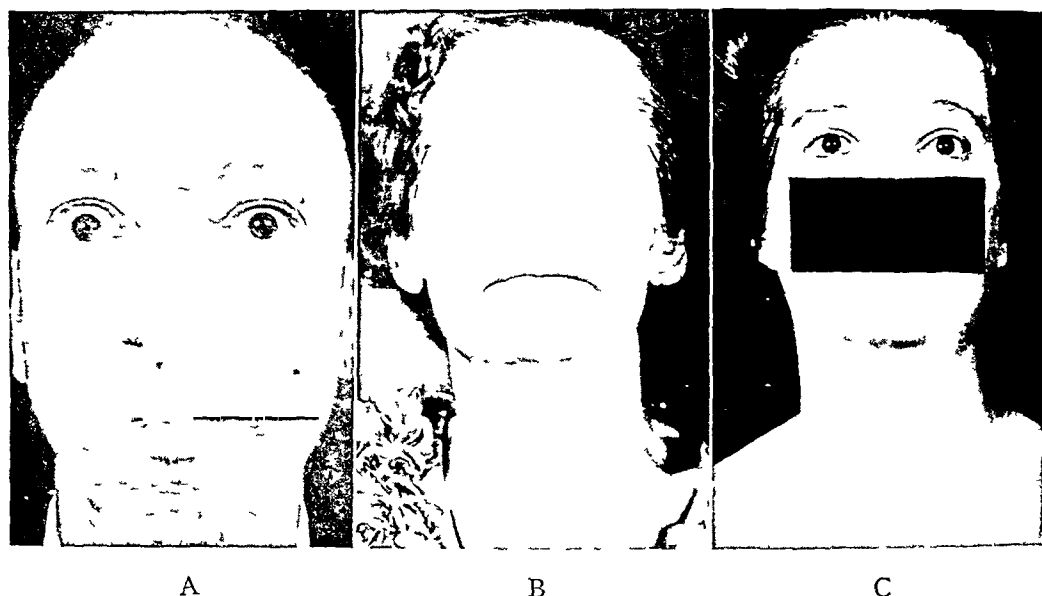


FIG 7—A Photograph of patient showing malignant exophthalmos. B Photograph of patient with local adenomatous nodule. C Photograph of patient exhibiting Graves' disease.

Clinical and pathologic studies have established with reasonable certainty that the bulging of the orbital contents is associated with swelling of the orbital muscles, connective tissue, and fat, together with a marked increase in lymphoid tissue (Naffziger and Jones,⁹ 1932). After prolonged edema of the muscles, replacement of muscle cells with fibrous tissue cells is a natural consequence. An hypothesis is offered that the edematous swelling of the orbital tissues is due to the water retaining effects of thyrotropic hormone in particular, and possibly of posterior lobe hormone as well. The lymphoid tissue increase is considered due to depression of the adrenal cortex which accompanies marked hyperthyroidism. Hyperthyroidism not infrequently occurs in patients with Addison's disease (Brenner,¹⁰ 1928) and (Crooke and Russel,¹¹ 1935).

THYROID-PARATHYROID INTERRELATIONSHIPS

Experimental data To investigate thyroid-parathyroid interrelationships dogs were used as experimental animals. They were kept in metabolism cages and fed dog chow and horse meat. The following operations were carried out on the hypophysis through the oral approach: (1) removal of the glandular and neural lobes (simple hypophysectomy), (2) removal of the adenohypophysis and the entire neural hypophysis (total hypophysectomy), (3) denervation of the neural hypophysis by section above the median eminence without removal of the adenohypophysis (puncture Type I), (4) simple hypophysectomy plus total thyroidectomy.

Two dogs were kept in cages as normal controls. Three dogs were simply hypophysectomized, two were totally hypophysectomized, two were punctured (Type I) and two were simply hypophysectomized and thyroidectomized.

The dogs were kept for periods of one to seven years before being sacrificed and completely autopsied. During this time none of the dogs showed variations in their serum calcium or serum phosphorus beyond the limits of normal. Analysis of the findings permit the following statements to be made:

1. Caging of normal dogs on the diet used did not lead to parathyroid gland enlargement.

2. Two years or more after simple hypophysectomy, after total hypophysectomy, after puncture, Type I, and after simple hypophysectomy plus thyroidectomy, definite enlargement of parathyroid glands occurred.

3. The loss of hypophyseal basophil cells, or their degranulation, is

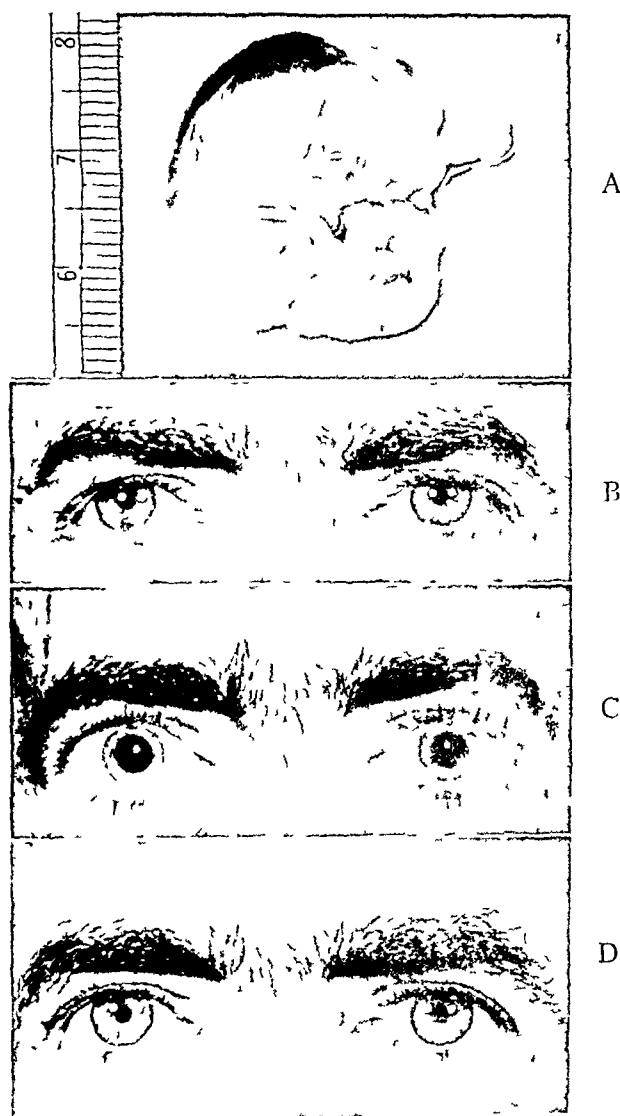


FIG 8—A Photograph of parathyroid adenoma removed at operation from patient shown in B, C and D.

B Photograph of patient's eyes 18 days after operation. Note eyes are normal. Pre-operative BMR -16 .

C Photograph of patient's eyes 28 days after operation. Note marked exophthalmos. BMR $+26$.

D Photograph of patient's eyes six months after operation. Note return of eyes to normal. BMR normal. Iodine administered for 10 days. No operation on thyroid gland.

associated with atrophic changes in the thyroid gland and with parathyroid enlargement

On this evidence it is concluded that the hypophysial basophile cells exert an inhibitory influence on the parathyroid glands. Their loss or degranulation permits parathyroid gland enlargement

Illustrative Case A white male, 36 years of age, was admitted to Barnes Hospital because of nausea, vomiting and weight loss of three years' duration. Nine months before admission lumps appeared on his lower right jaw and on his left tibia. His serum

NEURO-ENDOCRINE AND ENDOCRINE INTERRELATIONS

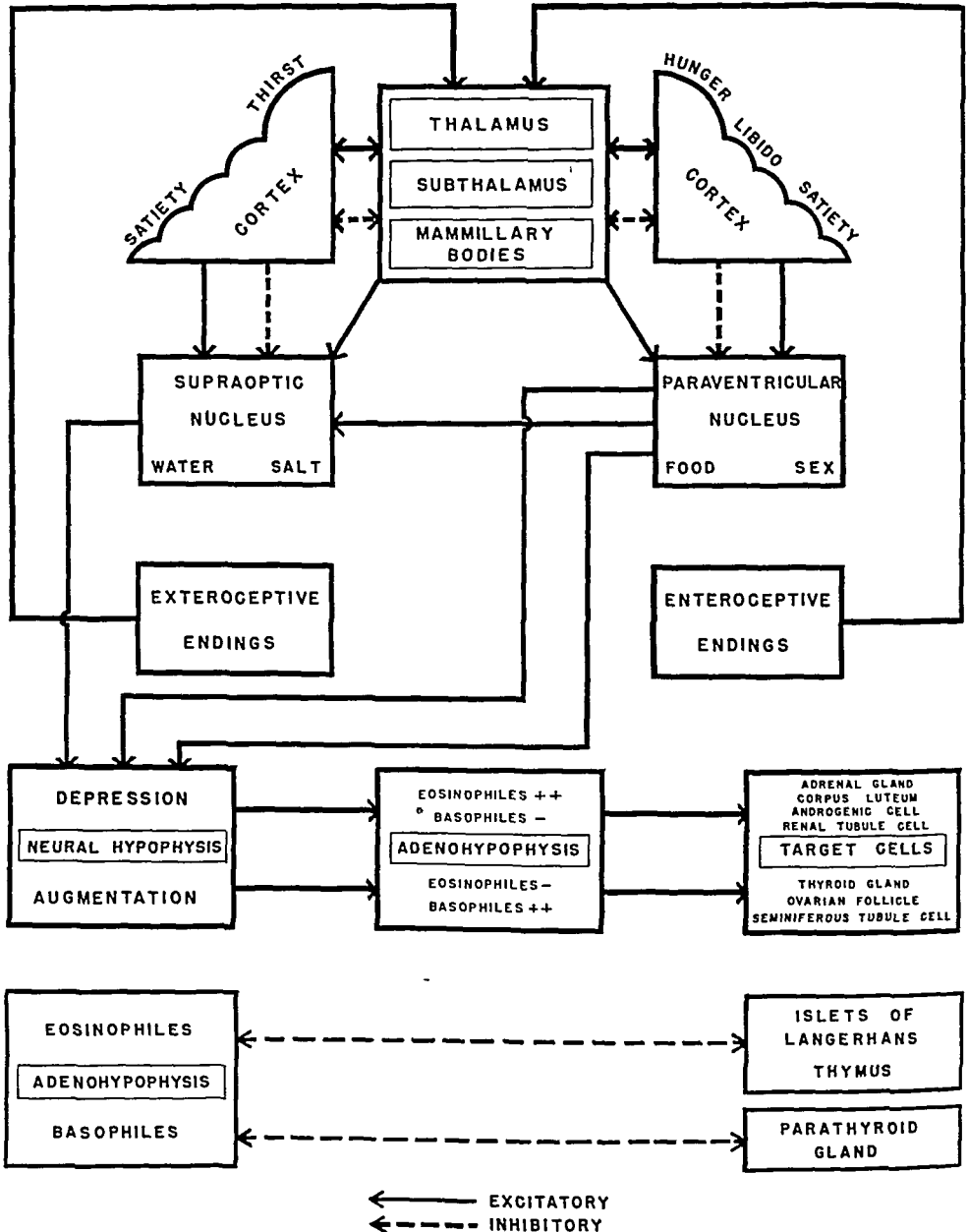


Fig 9—Diagram to show manner in which influences from the central nervous system, acting through the hypothalamus on the neural hypophysis, can effect changes in other endocrine glands

calcium was found to be 17.2 mg per 100 cc, his serum phosphorus 5.4 mg per 100 cc, alkaline phosphatase 26 Bodansky units, BMR -16 per cent, urine concentration to 1013 and urea clearance 59 per cent average normal. A biopsy of the tibia showed fibro-cystic disease of the bone. A diagnosis of a parathyroid tumor was made. On March 30, 1948, an adenoma of the parathyroid was removed (Fig 8). Following his operation the patient developed hyperthyroidism with exophthalmos (Fig 8). On May 7, 1948, his BMR was $+28$. No enlargement of the thyroid gland was evident. The patient responded rapidly to iodine. On May 17, 1948, his BMR was $+3$. He has remained well without additional treatment.

Comment The case demonstrates that hyperthyroidism with exophthalmos may develop following the removal of an actively secreting parathyroid adenoma. The explanation offered for this occurrence is that the overactive parathyroid adenoma had inhibited the hypophyseal basophile cells which was reflected in the basal metabolic rate of -16 . After removal of the inhibitory influence the basophile cells responded with a temporary overaction to cause the hyperthyroidism and the exophthalmos.

Additional support for the concept that depression of the hypophyseal basophile cells may lead to an increase in size of the parathyroid glands is found in a study of Cushing's syndrome (Heimbecker,¹² 1946). In this syndrome an adenoma of the parathyroid gland is not infrequently found. Basophile cell function is considered to be depressed because of the elevated blood cholesterol and decreased metabolic rate found in patients with Cushing's syndrome.

CLINICAL DATA

Prolonged experience with the surgical treatment of hyperthyroidism, together with observations on the specimens removed at operation, permit the deduction that hyperthyroidism may result either from overaction of cells localized in a nodule, or from a diffuse overactive acinar tissue with a varying degree of hypertrophy of the entire thyroid gland. In the first instance, clinical study fails to reveal evidence of a general disturbance of the endocrine balance in such persons. The primary cause of overactivity apparently is local, whereas in the instances where the thyroid gland is generally overactive there is invariably evidence of a generalized disturbance of endocrine balance. This is exhibited, among other things, by an alteration of adrenal gland and sex gland function.

Recent investigations of hyperthyroidism due to an overactive local nodule have been reported by Cope, Rawson and MacArthur¹³ (1947). Their demonstration that the thyrotropic hormone is concentrated in the cells of the overactive nodule, leaving the remainder of the thyroid gland relatively inactive, gives excellent support to the belief that the primary alteration is in the involved cells. Their evidence indicates also that the thyrotropic hormone stimulates the secretion of thyroid hormone by the involved cells, in fact, after a fundamental change has occurred in the adenomatous tissue its cells become more than normally responsive to the thyrotropic hormone. Experience with hypophysectomized animals in which marked thyroid atrophy occurs,

indicates that without thyrotropic hormone such altered cells would not continue to be overactive. Demonstration by the authors that radioactive iodine is concentrated in the overactive cells is of fundamental significance. It, too, supports the concept that the hyperthyroidism due to an overactive nodule is not associated with a generalized endocrine imbalance. Only when the primary disturbance is in the central nervous system and of a type which leads to overactivity of the hypophyseal basophile cells, with a consequent overproduction of thyrotropic hormone, does the disease become a generalized endocrine disturbance.

Hyperthyroidism is associated also with overaction of the autonomic nerve system "centers" of the hypothalamus. Among the signs and symptoms attributable in part to such action are tremor, tachycardia, irregularities of the pulse, hyperacidity, hypermobility of the intestines, and sweating. These signs may be produced experimentally by excitation of the sympathetic and the parasympathetic nervous systems. They may be seen also as effects of the administration of thyroid substance itself, except for sweating, which is entirely neurogenic in origin. Here, as elsewhere, biologic processes occurring in animals possessing a complex interrelationship between their nervous and endocrine systems may be initiated either by a neurogenic or by a humoral mechanism. Characteristically these mechanisms differ in the speed of their action. Neurogenically initiated effects are rapid in their development to be supported by the more slowly developing humoral influences.

HYPERFUNCTIONING SINGLE ADENOMA OF THE THYROID

Illustrative Case A 50-year-old white married housewife (Fig 7) entered Barnes Hospital because of a constant feeling of increased warmth, increased perspiration, nervousness and tachycardia. She had had a goiter for 15 years. This did not disturb her health until nine years ago, when her toxic symptoms began to manifest themselves.

Examination revealed a well localized nodule in the right lobe of the thyroid, the remainder of the thyroid gland was not enlarged. B. P. 170/70, BMR +31, blood cholesterol 270 mg per 100 cc, WBC 6470, percentage of circulating lymphocytes, 27.

The patient was treated with radioactive iodine. Her symptomatic response was dramatic, she gaining 20 pounds within seven weeks. Three doses of radioactive iodine totaling 25 millicuries were administered over a seven-month period before the basal metabolism returned to normal. By this time the nodule had reduced itself one third in size.

Comment The patient was considered to have a single adenoma of the thyroid on the basis of physical examination only. She was chosen to represent the single adenoma group because of her satisfactory response to radioactive iodine. The result would be anticipated from the findings of Cope, Rawson and MacArthur (1947, loc cit) which demonstrated that active adenomatous thyroid tissue has an avidity for iodine, almost to the exclusion of less active acinar tissue. The surgical removal of such nodules results in a complete and permanent cure of the patient, a gain indicating that the disease is due to the local disturbance in the thyroid nodule.

GENERALIZED HYPERFUNCTION OF THE THYROID GLAND

Illustrative Case A 16-year-old white unmarried female (Fig 7C) entered Barnes Hospital because of nervousness, tachycardia, sweating, increased appetite, instability and tremor present for six months. Amenorrhoea had been present for three months. A progressively enlarging goiter had been noted for two months.

Examination revealed diffuse enlargement of the thyroid gland. Pulse 110, BP 130/68. The skin was of fine texture and moist. The eyes were prominent, with some lid lag. Marked fine tremor of the fingers was present. WBC 6300, percentage of circulating lymphocytes 50, BMR +36. Plasma cholesterol was 120 mg per 100 cc.

After treatment with propyl thiouracil and iodine a subtotal thyroidectomy was performed. Three days after operation the patient menstruated normally. She has continued to do so normally. Microscopic study of the thyroid tissue removed showed marked generalized changes which have been found to be characteristic of overactive acinar tissue.

Since operation her symptoms and her exophthalmos have both regressed. Her basal metabolic rate three months after operation was normal.

Comment The high percentage of circulating lymphocytes is taken to indicate underactivity of the adrenal cortex. Studies of the vaginal mucosa before operation showed changes characteristically seen during active estrogen production. At this time the gonadotropic titer on a 74-hour urine specimen was 112 mouse uterus units. On the second day the post-thyroidectomy 24-hour urine specimen contained 6.2 M U U. The daily urine content for a 20 to 30 year old regularly menstruating female averages 3 M U U*. It is believed that the menstrual period occasioned in the immediate postoperative period was the result of the liberation of a luteinizing factor rather than to an excessive release of follicle stimulating hormone. This would be indicative of a restoration of balance between hypophysial basophiles and eosinophiles, because the latter are the source of the luteinizing hormone.

DISCUSSION

Of crucial importance in the chain of evidence supporting the present concept of the pathogenesis of hyperthyroidism is the demonstration by us that the hypophysial basophile cells secrete a hormone trophic to the thyroid gland. This finding is confirmed by Brodin¹⁵ (1946) who showed that in the rat, proliferation of the thyroid acinar tissue occurs on exposure to cold. In animals so treated a marked increase in the basophile cells of the glandular hypophysis occurs. He showed also that exposure to cold led to an increase in the amount of circulating thyrotropic hormone. Thus, both histologic and functional evidence is available to support adequately the evidence obtained in this laboratory indicating that the basophile cells of the glandular hypophysis are the source of the thyrotropic hormone.

The finding that prolonged administration of posterior pituitary hormone results in an increase of well granulated hypophysial basophile cells affords a mechanism whereby the pathogenesis of hyperthyroidism may be associated with augmented activity in the central nervous system, particularly the hypothalamus. Clinical experience supports such an association. Thus an analysis

* I am indebted to William H. Masters, M.D., for these analyses.

of the signs associated with hyperthyroidism, particularly in Graves' disease, shows that many of them are attributable in part to overactivity of the autonomic nervous system. The hypothalamus appears to be the chief regulating "center" for the control of both the autonomic nervous system and the endocrine system of the body. Clinical experience and the experimental evidence of Bronk, Pitts and Lairabee¹⁶ (1940) indicate that both the sympathetic and the parasympathetic systems can be depressed or augmented in their activity by fibers coming to the hypothalamus from the central nervous system. Its regulating influence on the endocrine system is indicated by the experimental results in the puncture dogs of a marked decrease in basophiles, and the opposite result of an increase in basophiles after the administration to normal dogs of posterior lobe hormone. Depression of the activity of the supraoptic and the paraventricular nuclei which innervate the neural hypophysis results in a decrease in the release of posterior lobe hormone and a decrease in the number of basophiles. The increase in the number of basophiles which follows the administration of posterior lobe hormone indicates that increased activation of the supraoptic and the paraventricular nuclei would result in such an increase of basophiles. The conclusion is warranted that the maturation of the glandular hypophysial basophile cells is under neurogenic control, by way of the neural hypophysis, regulated by fibers from the hypothalamus.

This interpretation is supported adequately by evidence herein presented and also by that of Biolin (1946, loc cit), who showed that section of the stalk of the hypophysis eliminates the increase of basophiles, and of thyrotropic hormone which follows exposure to cold of the unaltered rat. Therefore, thyrotropic hormone released on exposure to cold is under neurogenic control.

Other experimental conditions pertinent to our problem affecting hypophysial basophile cell maturation are the removal of the thyroid gland or of the ovaries or the testes. It is accepted generally that an increase in the number of basophiles follows removal of the thyroid gland or of the gonads. That the increase of basophiles which appears following these procedures is associated with an increased release of thyrotropic or of gonadotropic hormone has been shown by Addison¹⁷ (1917) by Smith, Severinghaus and Leonard¹⁸ (1933) and by Finnerty, Meyer and Marvin¹⁹ (1944).

Chouke, Friedman and Loeb²¹ (1935) showed that in the female guinea pig during the sexual cycle the proliferative activity, and presumably also the metabolic activity of the thyroid acini, is greater than in male animals of corresponding age. It is probable that the mitotic proliferation of the thyroid gland undergoes cycles which are correlated to the sexual cycle, the maximum in mitotic activity being low during the follicular phase. It rises during the lutein phase, reaching the highest point at approximately the fifth day of the cycle in the guinea pig, at a time when the uterine mucosa also reaches a maximum of proliferation.

Experimental and clinical evidence obtained in this laboratory indicates that ordinarily basophile cells are trophic to the ovarian follicles as well as

to the thyroid gland. It follows that conditions which augment thyrotropic hormone may also recognizably increase gonadotropic hormone activity. Following operations in which the thyroid or the gonads alone are removed, such activation need not occur, or if it does, it may be slight for the glands not removed. In hyperthyroidism, as seen in Graves' disease, both hormones apparently are released from the basophile cells.

It has been shown also that any augmentation of estrogen release increases the effect of posterior lobe hormone, particularly of the oxytocic fraction (unpublished data in this laboratory). Sex hormone influences on the central nervous system and on the maturation of the basophile cells of the glandular hypophysis presumably are significant in determining the higher incidence of hyperthyroidism in the female than in the male.

In a previous communication (Heinbecker²⁰ 1948, loc cit) it was shown that in the dog, depression of the supraoptic and the paraventricular hypothalamus nuclei affects a change in the cytology of the glandular hypophysis characterized by a preponderance of the eosinophile cells and a marked loss of basophile cells (Fig 9). Because of this imbalance changes are effected in the function of the other endocrine glands of the heart and of the kidneys, which result in the development of diastolic hypertension, obesity, decreased sugar tolerance, and arteriosclerosis. The incidence of these sequelae, and their severity, vary considerably because of factors not yet understood completely. The differences in bodily reaction to a given change in hormonal secretion, or imbalances between secretions, may be assigned at present only to a "constitutional factor." Essential hypertension is ascribed primarily to the consequences of a functional depression of the hypothalamic nuclei in persons so constituted that their adaptation response to the sum of the exteroceptive and interoceptive influences acting on their central nervous systems is a depression of the supraoptic and the paraventricular nuclei of the hypothalamus. Hyperthyroidism, on the other hand, develops in persons in whom the effect of the sum of the exteroceptive and the interoceptive influences is one of excitation of these same hypothalamic nuclei. From this, basophile, not eosinophile cell preponderance follows to result in the increased production of hypophysial hormones trophic to the thyroid, the ovarian follicles and the spermatogenic cells. There may be an associated depression of the hypophysial hormones trophic to the adrenal gland and to the progesterone and the androgenic producing cells. The two conditions are therefore opposite extremes in the range of variability of activity of the hypothalamic-hypophysial mechanism which serves as the chief regulator of hormonal balance in the body and which is itself subject to control by the higher levels of the central nervous system.

SUMMARY

Hyperthyroidism results from the release of normal thyroid secretion in excess.

The excess secretion may be derived from a localized adenomatous group of cells within the thyroid gland or from the normal secretory cells of the thyroid gland in general.

The primary disturbance, where localized overactivity exists, rests within the involved cells. The primary exciting disturbance for generalized overactivity comes from the hypophysial basophile cells whose secretion is trophic to the thyroid gland. Overactivity of the hypophysial thyrotrophic cells results primarily from an increase of the secretion of the neural hypophysis which is under nervous control through fibers coming from the supraoptic and the paraventricular hypothalamic nuclei.

Hyperthyroidism caused by increased activity of the normal secretory cells of the thyroid gland in general, occurs in persons so constituted that their adaptation response to the sum of their external and internal body stimuli is excitation of the supraoptic and the paraventricular nuclei.

Depression of the thyroid gland, the ovarian follicles, and the seminiferous tubule cells also increases the maturation of the hypophysial basophile cells by decreasing the normal inhibitory influence of these structures on such maturation.

Fluctuations in hypophysial basophile cell activity occur during puberty, menstruation, pregnancy, and the menopause. Increased estrogen secretion facilitates the action of the secretion of the neural hypophysis. These factors are significant in causing a higher incidence of hyperthyroidism in women than in man.

Exophthalmos, before chronicity is established, is a reversible phenomenon. It results from the swelling of the intra-orbital contents, particularly the muscles, the connective tissue and the fat. An accumulation of lymphoid tissue occurs also. The swelling is a result of water retaining influences of the hormone of the neural hypophysis and particularly of the thyrotrophic hormone. A depression of the thyroid hormone has a similar influence. The lymphoid tissue accumulation is a result of a depression of the adrenal cortical function, associated with the endocrine imbalance tending toward hyperthyroidism. A local susceptibility of the orbital tissue to the water retaining influences of the involved hormones is assumed.

The hypophysial basophile cells are inhibited by an excess of parathyroid hormone. The secretory production of the hypophysial basophile cells is inhibitory to the parathyroid gland. Removal of an actively secreting parathyroid tumor may permit overactivity of the hypophysial basophile cells and the production of hyperthyroidism.

Acknowledgments I am indebted to Dr. Mather Pfeifferberger for the exacting work of counting the cells in the glandular hypophyses reported on.

I am grateful to the Eli Lilly Company for the posterior lobe extract in protamine zinc, to the Winthrop Chemical Company for the preloban, to the Armour Laboratories for the thyrotrophic hormone, and to the Schering Corporation for the desoxycorticosterone pellets.

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DISCUSSION —DR FRANK H LAHEY, Boston, Mass I would not have you feel that from an investigator's point of view I think I am competent to discuss this paper—so informative interesting, and so valuable in clearing (in my mind) some of our uncertain conceptions of the origin of hyperthyroidism

On the other hand, many of you may not be as interested as I have been in how and why hyperthyroidism develops Having literally grown up with it from the stage when we knew next to nothing about it, it is fascinating to see various fundamental facts related to development of this disease each year become better and better revealed, until we now have a well-connected conception of the origin of hyperthyroidism This paper supplies, for me, some of the links which have been missing up to now

We have for a number of years known of the interrelationship of the anterior pituitary and its thyrotropic stimulating hormone with hyperplasia of the thyroid and the depressing influence of an increased production of thyroxin on what we thought was the anterior pituitary

It has been known for a number of years that there are neural pathways between the hypothalamus and the posterior pituitary, but the missing link has been the lack of demonstrable neural pathways connecting the hypothalamus or the posterior pituitary with the anterior pituitary. We now have revealed at least a more complete picture of the origin of this disease which has been so confusing to all of us in the past

The history of the clarification of many of the beclouded features of hyperthyroidism has been a fascinating one, and this appears to be one of the last links to complete the chain

In this chain of events blood iodine studies have been extremely interesting, particularly since we have learned to fractionate iodine into its organic and inorganic fractions. We have learned from these studies why certain things happen which we knew happened but previously we did not know how. It was through blood iodine studies, when we began to fractionate iodine, that we were able to demonstrate that the thyroid storms, which we assumed were due to increased outputs of thyroxin, were truly due to this, as could be demonstrated by the marked increase in organic iodine (the hormonal fraction) within two hours after the operation. It was possible to demonstrate that the intake of blood through the artery contained a lower organic iodine fraction than did the output of blood containing the hormonal factor in the veins. And now something which we have assumed for a great many years has been demonstrated microscopically by a young South American working at the Massachusetts Institute of Technology, Dr. de Robertis, who by freezing methods and staining has been able to demonstrate the bipolarity of the thyroid acinar cell

We have known in the past that there have been periods of secretion and rest in the thyroid. We could demonstrate by thyroid involution and distention of the thyroid acini that there were periods of activity, and by the high columnar and crinkled type of epithelial cells that it was hyperactive, but it remained for him to be able to stain the colloid which contains the thyroxin, and to demonstrate its extrusion through the periphery of the cell into the capillaries that run along the external portion of the cell, and so on into the blood stream

Through his work, too, was revealed the enzymatic process called the peroxidase process in the acinar cells, which may play at least some part in the final synthesis of thyroxin. It is now also possible to be better aware of how thyroxin is probably synthesized, first existing in the thyroid as an iodide, then converted into free iodine and joined with tyrosine to form diiodotyrosine and then synthesized further to the final stage of thyroxin. It is here that this paper of Doctor Heinbecker is so interesting to all of us who have been concerned with thyroid disease over the years. It is the final development of something that we have all known presumably existed, that is, the relationship between the paraventricular and supraoptic nuclei in the hypothalamus and the stimulation of the basophils in the anterior pituitary, thus to produce the hyperplasia, which in turn produces the excess of thyroxin associated with hyperthyroidism

Finally, I think that perhaps the most valuable development in recent years, for which we owe so much to Astwood, MacKenzie and various others, is the making available of the antithyroid drugs which have literally converted these patients coming to surgery to completely nontoxic states and which have done away completely with the danger of table deaths, postoperative reactions, and all the harrowing events which used to go with surgery of patients still in an intensely toxic state. I would like to tell Doctor Heinbecker how much I have enjoyed listening to this delightful presentation which so helps to clarify a situation that has not been completely clarified before

DR WILLARD BARTLETT, JR, St Louis, Mo (guest) Let me express my appreciation of the opportunity to speak today, and to congratulate Doctor Heinbecker on his beautiful presentation. I cannot refrain from making a few remarks about exophthalmos which are prompted by some of his statements.

I have repeated in the past, until I am afraid some of you are tired of hearing it, that until one with an exophthalmometer regularly examines the eyes of every patient with a thyroid disorder and records the findings at regular intervals throughout the course of the disorder, whether it be hypothyroidism primarily or hyperthyroidism to start with, it is very hard to evaluate what is happening to the eyes.

I want to assure you that one's impressions from looking at the eyes, as to how much exophthalmos, if any, is present, or whether the eyes are protruding more or are receding as time goes on, are quite worthless. One can measure proptosis only with an exophthalmometer.

It is most deceptive, and, as a matter of fact, the impression one gets that exophthalmos is present or that it is increasing from time to time, is due largely to the width of the palpebral fissure and to the behavior of the lids themselves. I give this to you for what it is worth, those of you who are also seeing these patients frequently.

In 1934, before the Western Surgical Association meeting in St Louis, I recorded some of the things upon which Doctor Heinbecker has commented today. Those of you who are old hands at thyroid surgery prior to twenty years ago, will recall that postoperative increase in exophthalmos was ordinarily held to be due to persistent or recurrent hyperthyroidism. It was in the late 1920's and early '30s that we had a number of such instances in patients who, to my bewilderment, proved to be hypothyroid after mature study.

In these cases, reported at the Western Surgical Association, it was learned then that restoring them to normal thyroid balance by thyroid feeding resulted in a prompt regression of the exophthalmos in those patients in whom the exophthalmos had been present for very brief periods. In those in whom exophthalmos had been present for months, little regression occurred, and it was postulated at that time that the pathology involved was one of early edema, and lymph edema, as a forerunner of myxedema in the orbital tissues, which was reversible early by thyroid feeding, but which, if allowed to persist, went on to fibrosis, leading to the picture of the orbital contents described by many individuals (among them Doctor Naffziger) who had done various types of operation for decompression of the orbit in late, long-standing exophthalmos.

I throw out also the comment that there is an early increase in proptosis in nearly all patients after thyroidectomy, no matter what their original measurements may be. This I have recorded previously, and it has been confirmed in a perfectly splendid series of studies from the Mayo Clinic, published within the last two or three years, given the Award of the American Goiter Association a couple of years ago. I am sorry I cannot give you the exact reference.

DR PETER HEINBECKER, St Louis, Mo. I wish to thank those who discussed my paper, particularly Doctor Lahey. His favorable attention to this work will expand the attention given to our humble efforts to a much greater degree than he realizes.

I also wish to thank Doctor Pfeifferberger, Doctor Fischer, and Miss Dennis, fellow workers in my laboratory, for the help they have given me in making these facts available to you.

TRANSMETATARSAL AMPUTATION FOR INFECTION OR GANGRENE IN PATIENTS WITH DIABETES MELLITUS*

LELAND S McKITTRICK, M D , JOHN B McKITTRICK, M D
AND THOMAS S RISLEY, M D

BOSTON, MASSACHUSETTS

FROM THE NEW ENGLAND DEACONESS HOSPITAL

This might be considered a report of progress in the surgical management of lesions of the lower extremities in patients with diabetes mellitus. Fifteen years ago in a paper before this Association, one of us¹ in analyzing the deaths following amputations for gangrene, pointed out that the mortality rate was 13.7 per cent, that about 10 per cent of these patients died as the result of uncontrolled sepsis, that if and when some mechanism other than surgery was developed for the control of infection, we might anticipate a mortality following major amputation of about 5 per cent.

Chemotherapeutic agents and the antibiotics have made it possible to control invasive infection, and the mortality rate has fallen as anticipated (Table I). This is of particular significance in the management of these patients with diabetes mellitus because this control of invasive infection invited a different approach to a selected group of cases. With the danger of ascending infection and septicemia eliminated, it might now be practical to consider each foot on the basis of its arterial supply. In selected cases, amputation might now be performed at a more distal level with safety and a reasonable chance of success. There was reason to believe that if all or part of the toe was gangrenous, amputation through the foot just proximal to the heads of the metatarsals would be more likely to succeed than removal of the toe alone. Such an amputation would, in addition, offer the patient protection against subsequent involvement of the remaining toes, and would give him a useful foot.

In 1944 we did our first transmetatarsal amputation for gangrene of a toe in a diabetic patient. The lesion in this patient was one for which we had previously considered amputation through or above the mid-lower leg as the operation of choice. The operative wound healed promptly. There have been 215 such amputations done at the New England Deaconess Hospital up to January, 1949,[†] and sufficient time has elapsed to permit a study of these cases in an attempt more clearly to delineate the indications and the technic, and to review the early and late results.

* Read before the American Surgical Association, St. Louis, Mo., April 22, 1949.

† We are indebted to Drs. T. C. Pratt and C. C. Franseen for permission to include patients operated upon by them and for their cooperation in obtaining follow-up data on their patients.



FIG 1 —Gangrene of toe (A) and lateral aspect of base of fifth toe (C) Successful transmetatarsal amputation in these two patients (B & D)

INDICATION

Our experience will permit only a discussion of the anatomical indications. Removal of a toe, especially the great toe, with its metatarsal head, alters weight bearing and increases the vulnerability of the remaining toes, therefore, we prefer the relative security of the transmetatarsal amputation. Factual

TABLE I—*Mortality Following Major Amputations 1923-1949,
New England Deaconess Hospital*

Period	No Cases	No Deaths	Mortality (%)
1923-1941	680	93	13.7
1941-1949	358	20	5.5



FIG 2—Exemplifying total excision of open wound and primary closure of transmetatarsal amputation. (A) Initial lesion, (B) local excision of initial lesion and drainage of soft tissue infection, (C) hospital result 18 days post transmetatarsal amputation.

evidence to support this preference is not at hand but, with this thought in mind, we have advised this procedure for the following indications:

1. Gangrene of all or part of one or more toes, providing that the gangrene and accompanying infection *have become stabilized* and the gangrene has not involved the dorsal or plantar aspect of the foot (Fig. 1).

2. A stabilized infection or open wound involving the distal portion of the foot, when total excision of the infected area with primary or delayed closure can be accomplished (Fig. 2).



FIG 3—Neurogenic foot with destruction of third and fourth metatarso-phalangeal joints. Partially closed amputation with subsequent secondary closure of plantar flap and pinch grafts to dorsum. Area of anesthesia totally excised (A) and (B) presenting lesion, (C) transmetatarsal amputation, area of local infection left open, (D) delayed suture of plantar defect and pinch grafts to dorsal granulating wound nine days post-amputation

3 An open, infected lesion in a neurogenic foot (a) as a curative procedure when the entire area of anesthesia can be excised (Fig 3), or (b) as a delaying procedure when the area of infection can be excised but the line of incision is through the area of anesthesia (Fig 4)

GANGRENE

We know of no way to determine accurately that a transmetatarsal amputation will be successful in a foot whose arterial blood supply is deficient. If the process is stabilized, and if gangrene and infection are well demarcated, there is a borderline group where only trial and error will give the final



FIG 4—Recurrent ulceration on amputation stumps in anesthetic plantar flap. Good circulation and diabetic neuropathy.

answer. With experience we become increasingly accurate in the estimation of the potentialities of the circulation of a given foot, but we are not able always to foretell the outcome with accuracy. We are sometimes pleasantly surprised to obtain early and prompt healing (Fig 5), just as we are occasionally disappointed to find necrosis and delayed healing or failure to heal (Fig 6). If the gangrene has extended onto the dorsal or plantar aspect of the foot, only rarely will this procedure be successful. Occasionally an area of gangrene may extend slightly onto the medial or lateral aspect of the foot and can be excised without jeopardizing the result (Fig 1). On the other hand, when the circulation in the foot is adequate, infection may extend well onto the foot and not contraindicate the operation (Fig 3).

Excision of area of infection. One of the most satisfactory by-products of this operation for gangrene has been its adaptation to a group of patients where the circulation in the foot has been reasonably good, but where the pre-

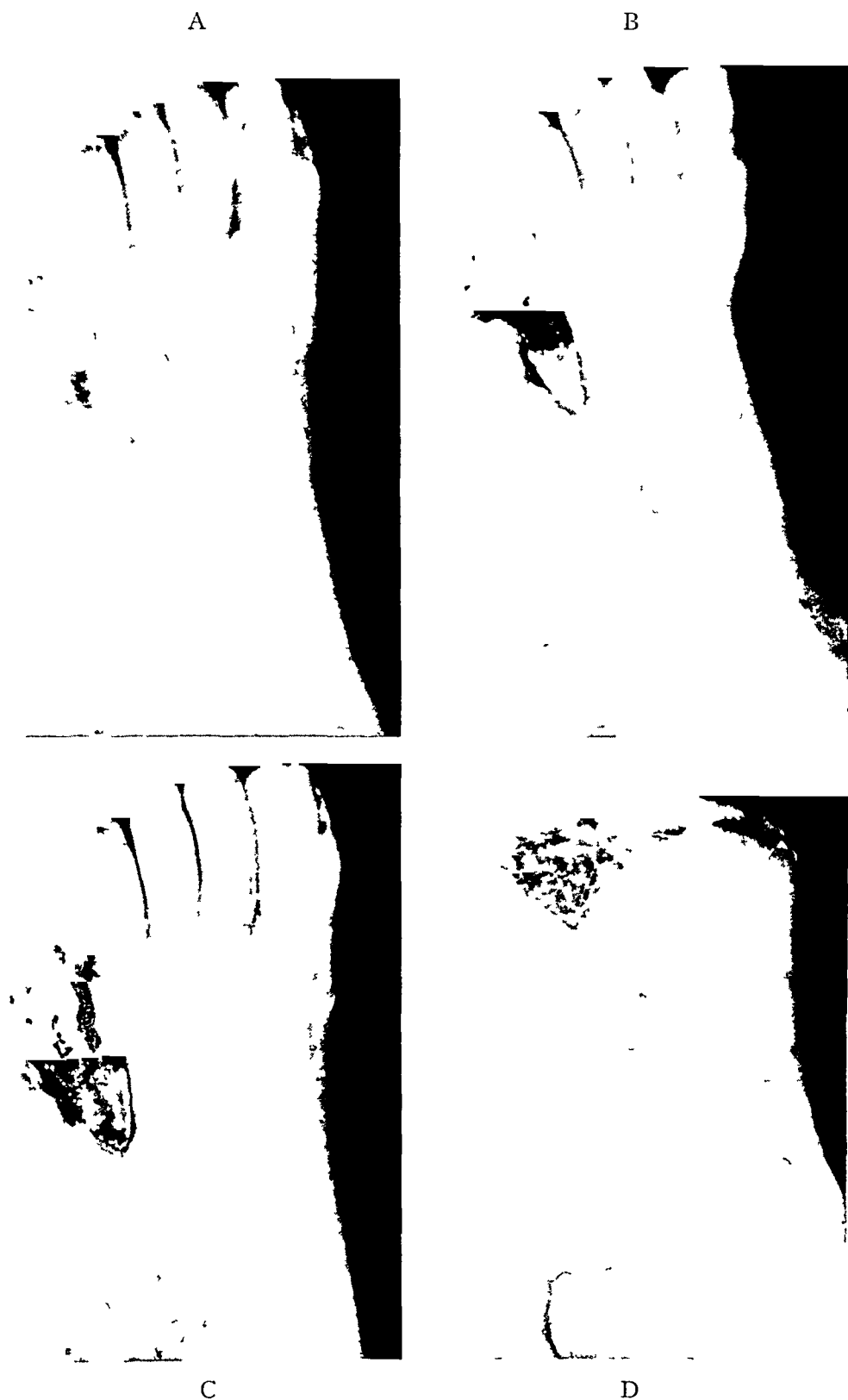


FIG 5—Successful transmetatarsal on an extremity with very poor circulation. A failure was anticipated. (A) presenting lesion showing gangrene of the fifth toe, ulceration onto dorsum with diffuse, surrounding cellular reaction, (B) and (C) progressive localization and demarcation, (D) hospital result 21 days post-amputation. The defect on the dorsum is not yet healed.

dominant factor has been infection. We have now had a modest number of patients who entered the hospital with severe local infection, usually involving one of the metatarsophalangeal joints and not infrequently the web space. Initial drainage with or without amputation of one or more toes has been carried out in order to control the infection. After the process has become stabilized it has been possible to do a transmetatarsal amputation, excising the entire granulating area. The edges of the newly made wound are carefully approximated with steel wire (Fig 2). In a few of these cases a small segment of the wound has been packed loosely with gauze and allowed to heal by secondary intention. In others, a granulating area on the dorsum of the foot has then been covered with pinch grafts removed from the amputated segment (Fig 7).



FIG 6—Immediate failure in a patient with poor circulation but in whom a successful result was anticipated (A) presenting lesion, (B) and (C) progressive dorsal necrosis within 12 days postoperatively. Supracondylar amputation done three days after (C).

Neurogenic lesion These lesions are the most disturbing and baffling of all of the lesions that we see in this group of patients. In most instances there is an open, infected area on the plantar aspect of the foot, surrounded by an area of thick callus, and frequently leading into a metatarsophalangeal joint. There is partial or complete anesthesia to pin prick in the involved area. The arterial supply is usually adequate. A variety of surgical procedures has been utilized for this condition and healing is usually prompt. In almost all instances, however, there will be recurrence in spite of any precaution we have been able to take, unless all of the anesthetic area on the plantar aspect of the foot can be excised. If the incision on the plantar aspect is through skin

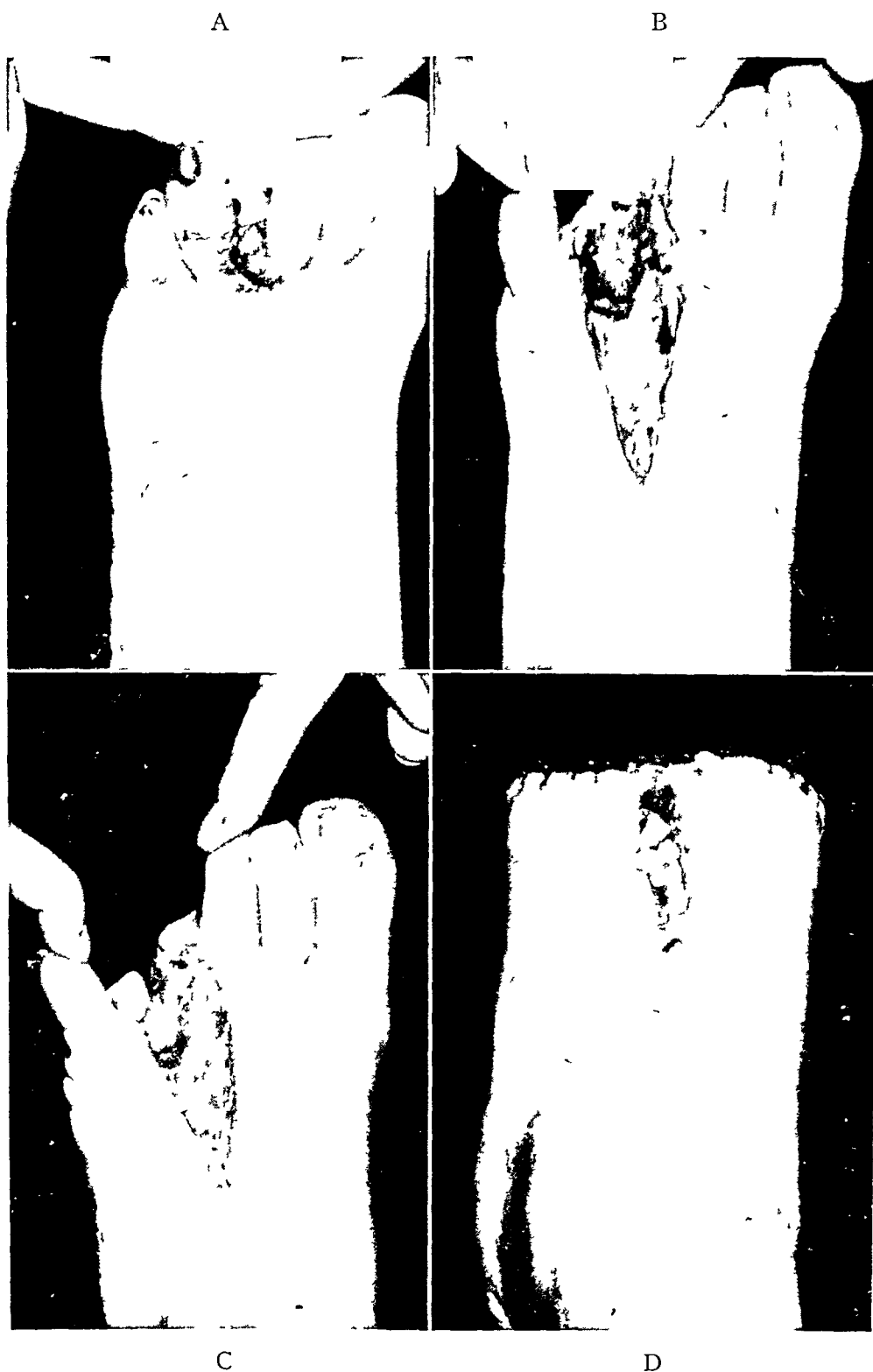


FIG 7—An example of preliminary drainage of infection followed in 23 days by closed transmetatarsal amputation. The pinch grafts were taken from the amputated forefoot. (A) presenting lesion, (B) preliminary drainage, (C) stabilized, open wound immediately pre-amputation, (D) hospital result 10 days post-amputation.

with normal sensation, not only will healing be complete, but a good result may be expected. Otherwise, almost without exception, the result will be merely a delaying one (Figs 3 and 4)

PREPARATION FOR OPERATION

Probably the most important single factor favoring a successful outcome in a patient with borderline circulation is selection of the proper time for operation. Just when this is we are not certain, but every effort should be made to

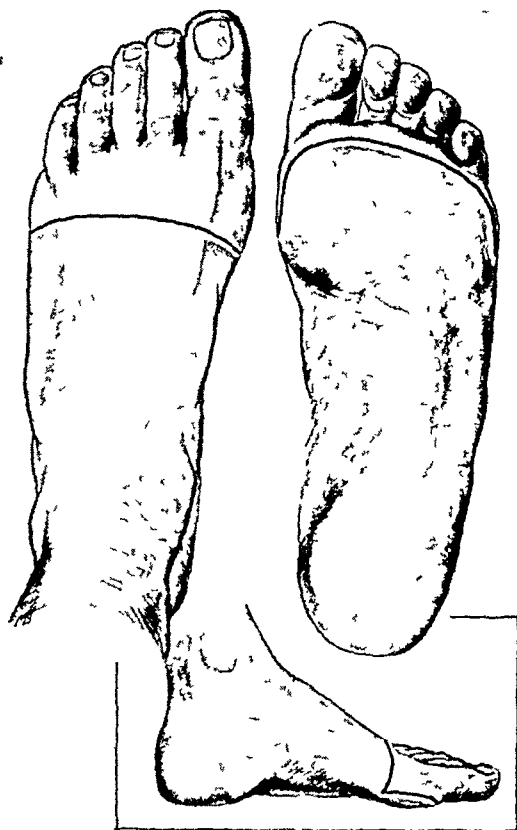


FIG 8—Illustration showing line of incision. Note long plantar flap

do the operation after the gangrene and infection have demarcated. We know from past experience that patients entering the hospital with severe pain will continue to benefit from the hospital routine for a period of two to three weeks. We have, therefore, taken approximately three weeks as the period during which adjustment of the local circulation may be expected to take place. Maximum improvement should then be evident and the patient ready for operation. Patients are given penicillin, usually a preparation of procaine penicillin G, 300,000 units once or twice daily if infection is present in association with the area of gangrene. When infection has been controlled, usually in five to seven days, penicillin is stopped. Buerger exercises are started and continued for approximately two weeks. Patients with more favorable circulation may be operated upon at an earlier time. During this period of

preparation the general condition of the patient is supported, transfusions of blood are given to obtain a hemoglobin of 13 Gm or more, the diabetes is adjusted and every effort is made to have both the patient and the local area in the best possible condition for operation. During the 24 hours before the time of operation, the patient is given 600,000 units of the procaine penicillin G. This is continued for four days postoperatively.

TECHNIC OF OPERATION

A low spinal anesthesia has been used for all of these operations. The lines of incision are shown in Figure 8. The long plantar flap is important because experience has shown that the blood supply to this flap is much better

than that to the dorsal flap. Great care is taken to make the incisions decisive, using a sharp knife which is changed after the skin incision has been made. There is no undermining or dissection of the dorsal flap, but the incision is carried directly down to the bone. Dissection of the plantar flap is kept close to the underlying bone. Each metatarsal is divided just proximal to its head with bone forceps. All sesamoid bones are removed. No special attention is given to the tendons. Careful hemostasis with a minimum of trauma is essential. Closure is carried out in one layer using a serum proof suture material to approximate the skin edges. Fine (No. 38) stainless steel wire has proved the most satisfactory in our hands. Closure of the wound is started from each end, to insure accurate approximation at these two vulnerable areas. There must be no tension to the suture line, nor should the flaps be redundant. The wound is not drained.

POSTOPERATIVE CARE

An important feature of the postoperative, as well as the preoperative care is the position of the patient in bed. In order that the extremity not be blanched and the veins remain full, the head of the bed is elevated so that the heart is always at a slightly higher level than the most distal portion of the feet. This dependency may be accomplished either by placing shock blocks under the head of the bed or by cranking the head of the bed up to the desired level.

Patients are kept on bed rest in the above fashion for a period of two to two and a half weeks after amputation. One half the stitches are removed about the ninth day, and the remainder between the twelfth and fourteenth day. In preparation for ambulation Buerger exercises are started ten to 15 days postoperatively. Mobilization is begun gradually, starting with one minute three times a day. Buerger exercises are continued, and the amount of walking permitted is gradually increased. Usually the patient is ready for discharge from the hospital three to four weeks after operation. The average postoperative stay for the entire group has been 30 days.

HOSPITAL RESULTS

A total of 215 patients have been operated upon up to January 1, 1949, (Table II). There were two hospital deaths, a mortality of 0.9 per cent. Healing was complete in 155 patients at the time of discharge. Sixty patients failed to heal, and of this group, re-amputation was done at a higher level in 27 patients, with prompt healing in all but one. This latter patient represents one of the fatalities. Thirty-three patients left the hospital with wounds not completely healed.

Fatal Cases Both patients died of coronary thrombosis. One was a 77-year-old diabetic of 12 years' duration who died on his 48th hospital day, ten days after his transmetatarsal amputation. Preceding the amputation a prostatectomy had been done for urinary retention. The second, a 71-year-old

woman, who had diabetes for 24 years, died on the 24th hospital day. An unsuccessful transmetatarsal amputation had been followed by a supracondylar amputation ten days before death.

Failures. Supracondylar amputation had been advised for five of this group of 27 patients. All of these patients developed early progressive necrosis along the suture line. Most of them had severe local pain in association with the necrosis.

TABLE II—Hospital Results Following Transmetatarsal Amputation

Indication for Operation	Cases	Healed	Unhealed	Re amputation	Died
Gangrene	145	94	25	26	2
Excision of Infection (neuropathy)	55	46	8	1	0
Excision of Infection	15	15	0	0	0
Total	215	155	33	27	2



FIG 9—Typical dorsal flap necrosis. Subsequent surgical revision was done three and one-half months later with primary healing.

Careful review of the available data does not indicate how a more accurate decision might have been reached. In each case failure was apparently due to arterial insufficiency. A possible exception was a patient with excellent collateral circulation but with no pulsations noted below the level of the femoral artery. This patient was sensitive to penicillin, and is the only patient in the entire series who was operated upon without the protection which this would have afforded. He is also the only patient in this series who developed invasive infection. It was our belief that penicillin would have permitted healing per primum. Rest pain was present in 47.5 per cent of these patients in contrast to 18.1 per cent of the remaining 188. When rest pain

does not entirely disappear during the period of preparation, the prognosis is very poor.

Local Complications. Fifty-three patients in addition to those already discussed, did not heal per primum. Twenty of these were healed at the time of discharge from the hospital. Eight of these patients had a minor separation of skin edges. In the remaining 12 patients, partial primary closure of the wound was followed by secondary suture, skin grafting, or healing by second intention.

The most important local complication in this group of patients was the development of a triangular area of discoloration on the dorsal flap (Fig 9) which occurs within 10 or 12 days after operation. In many instances this was transient and did not interfere with primary healing. In 33 patients, the discoloration progressed to necrosis of a segment of the dorsal flap, which involved the skin and subcutaneous fat, and which had not healed at the time of discharge from the hospital. If this necrosis is not too extensive, and if it demarcates early, there will be gradual separation of the necrotic tissue. This may take many months, during which time the patient is up and about. In selected cases, after complete separation of the slough, the defect may be closed by excision of the open area, shortening of the underlying metatarsal shaft or shafts, and careful approximation of the skin edges.

LATE RESULTS

Anatomical One hundred and fifty-five patients left the hospital with their stumps completely healed. We have been unable to learn the present condition

TABLE III—*Late Results Following Transmetatarsal Amputation, Stumps Healed at Time of Discharge*

Indication	Cases	Recurrent Ulceration	Re amputation
Gangrene	88	10	6
Excision of infection (neuropathy)	43	14	1
Excision of infection	15	0	0
Total	146	24	7

of nine of these patients. Twenty-four, or 16 per cent of the remaining 146, have had subsequent trouble (Table III). In ten of these patients the amputation had been done for gangrene. Three of these have developed a small area of necrosis at the medial or lateral corner of the scar. A fourth has a painful fissure of the heel. Six patients have survived successful amputation at a higher level necessitated by further gangrene. These six patients all had useful limbs for a minimum of one year (average 18.7 months). In the neuro-pathic group 14 patients have recurrent ulcerations at a weight-bearing point. One developed a callus and ulceration underlying a bony spur which developed at the transected end of the second metatarsal. This patient was well three months after excision of the spur. Re-amputation was necessary in one patient in this group, a 31-year-old diabetic with excellent circulation. He remained well for one year, then recurrent ulceration and intractable infection resulted in higher amputation.

Thirty-three patients left the hospital with the stump unhealed. Four of these healed in from two to ten months, but their present condition is unknown. Of the remaining 29 patients (Table IV) 13 have subsequently

healed Five of these had a successful revision of their stump (original amputation for gangrene) and in eight, healing has taken place by secondary intention In six of the ten patients who remain unhealed the appearance of the local lesion would suggest that ultimate healing and a satisfactory result should occur In the six patients who have been re-admitted to the hospital and survived amputation at a higher level the intervals between the two amputations have varied from two to ten months At no time did healing take place in this group

Functional Results We can only report upon the function of the transmetatarsal stump as it pertains to this elderly group of people (average age 61 5 years) whose physical activities are of necessity somewhat limited No patient considered his or her activities to be limited because of the loss of the distal portion of the foot There is a lack of forward balance Some patients report that in walking at a rapid pace the foot tires more easily than formerly All patients walk without a limp Those with bilateral transmetatarsal stumps (19 patients) use a shortened stride In all cases this stump has fully met the daily requirements of this group of patients and we feel justified in classifying the functional results as "excellent"

TABLE IV—*Late Results Following Transmetatarsal Amputations, Stumps Unhealed at Time of Discharge*

Indication	Cases	Healed	Unhealed	Re amputation
Gangrene	22	8	8	6
Excision of infection (neuropathy)	7	5	2	0
Excision of infection	0	0	0	0
Total	29	13	10	6

Prosthesis With but few exceptions these patients have been discharged from the hospital without any special type of shoe The toe of the shoe of the amputated foot has been filled with lamb's wool to lessen the tendency of the shortened foot to slip forward

Three patients with unilateral transmetatarsal amputations have had special inner soles made and report that they are very satisfactory This inner sole consists of a flexible steel plate with the space which the forefoot would have occupied filled with rubber foam This inner sole is not unlike that described by Bates² It has given comfort to the end of the amputation and has stiffened the sole, both of which are important features From this very limited experience it would seem to us that perhaps this may be the simplest and most satisfactory appliance

Five other patients with unilateral amputations have had a short, narrow, flexible steel plate inserted between the outer and inner sole of the regular shoe This steel plate extends to the level of the transected metatarsals, and minimizes the annoyance resulting from the flail-like action of the distal

empty portion of the shoe. This seems a more expensive way to handle the problem and probably no more satisfactory than a well-constructed inner sole. One ingenious patient with a unilateral amputation, a retired cobbler, simply had a cobbler friend do what amounted to a transmetatarsal amputation of his old shoe. This, he says, has been perfectly satisfactory.

All of the patients with bilateral amputations use custom-made short shoes. None of this group has used a shoe of the old size with specially constructed inner soles as described above. It is possible that such a solution would be satisfactory, and if so, the expense of having special shoes made each time a new pair is required would be eliminated. We are impressed that so few of these patients have felt the need for custom-made shoes.

TABLE V—*Summary of Results*

	Cases	% Total	Av	Follow up (Months)	
				Max	Min
Satisfactory*	135	67	28.5	57	7
Unsatisfactory†	32	16	20.8	56	4
Failures‡	35	17			
Total	202	100			

*Nineteen patients died at intervals of 8 to 54 months after discharge from the hospital of conditions not related to the amputation.

†Four patients died at intervals of 14 to 35 months after discharge from the hospital of conditions not related to the amputation.

‡Includes the 2 operative deaths.

Summary of Results. If healing has been complete and the amputation stump does not limit the patient's activities, we have classified the result as "satisfactory." If complete healing has not taken place, or if there has been recurrent trouble in relation to the stump but the patient is ambulatory, we have considered the result "unsatisfactory." If healing did not occur, and the open area has progressed resulting in amputation at a higher level, we have called this result a "failure."

The present condition of 202 patients is known (Table V). Thirty-five, or 17 per cent, of these (including the two who died) are failures. Thirty-two (16 per cent) have had one or more of a variety of local symptoms, but still retain limited use of their extremities. These we have considered as unsatisfactory. We feel that the remaining 135 patients, or 67 per cent of the entire group whose present condition is known, have had satisfactory results following their transmetatarsal amputations.

SUMMARY

1. Two hundred and fifteen transmetatarsal amputations have been done from July, 1944, to January 1, 1949, with two hospital deaths, both due to coronary thrombosis.

2 Thirty-three of these failed to heal, and came to amputation at a higher level

3 The present condition of the remaining 174 patients who left the hospital with a transmetatarsal amputation is known. One hundred and thirty-five of these are completely satisfactory. In 32 patients the end result is still undetermined and is regarded as unsatisfactory. Seven patients have come to higher amputation after complete healing for a minimum of one year.

4 The functional result has been excellent in all successful cases. Most patients with unilateral amputations use lamb's wool in the toe of their own shoe. Three patients use an inner sole insert with a rubber toe, which is probably the best, and five patients use a flexible steel bar between the outer and inner sole.

5 Custom-made short shoes are used by all patients with bilateral amputations, and this is regarded as a satisfactory solution.

6 We consider the results very gratifying and believe amputation at this level to be a major contribution to the management of this group of patients.

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DISCUSSION—DR LOUIS G HERRMANN, Cincinnati, Ohio. At the Cincinnati General Hospital we have employed, since 1934, the various conservative amputations through the foot for gangrene of the toes due either to arterial disease or to infection. We agree with Doctor McKittrick and his associates that many lives and many limbs can be saved by such procedures, but we differ with them slightly on certain technical aspects of the operation. It has been our experience that the transmetatarsal amputation gives the most serviceable stump of any of the amputations through the foot. We have allowed the end of the stump to remain open until a healthy granulation tissue base developed, then secondarily closed it by split thickness skin grafts, rather than make large skin flaps and close the stump at the primary operation. In patients without arterial insufficiency, the primary closure of the stump can usually be done safely.

Doctor Furste and I published the end-results of transmetatarsal amputations in 91 patients who were subjected to this procedure between 1934 and 1947. Of these patients, 37 per cent obtained an excellent or good result and a useful weight-bearing foot.

The antibiotics and chemotherapeutic agents have enabled us to control local infection so our future series should present an even higher percentage of useful weight-bearing feet after transmetatarsal amputations. Doctor McKittrick has demonstrated the value of conservative amputation in the diabetic patient and we are in agreement that these operations should be performed more frequently in patients with localized gangrene of the toes.

DR MICHAEL E DEBAKEY, Houston, Texas. I should like first to express my grateful appreciation to Doctor McKittrick and his associates for directing our attention to this valuable procedure. There are two facts that are particularly impressive in emphasizing the value of this procedure, first is the salvage of functioning extremities, and second is the strikingly low mortality. Those of us who have long been interested in peripheral vascular disease can fully appreciate the great improvement in both mortality

and morbidity which has been achieved by Doctor McKittrick and his associates, particularly in this older age group of patients with diabetes. Only about ten years ago the case fatality rate in the surgical management of such cases was as high as 30 to 40 per cent, with emphasis being placed on amputation above the knee. In striking contrast with these results Doctor McKittrick and his associates reported a case fatality rate of about one per cent. In addition, the patients were given functioning extremities. Thus, they have literally attained the salvage of both life and limb.

On the basis of our experience with this problem, there are two questions I should like to ask Doctor McKittrick. First, were there any differences in the results obtained between the diabetic and the non-diabetic group of patients with arteriosclerosis? I raise this question because in our experience it was observed that, if anything, somewhat better results may be obtained in the diabetics so long as the diabetes is properly controlled.

Secondly, I would like to ask what experience have they had in combining this procedure with sympathectomy. In our experience, sympathectomy has appeared to be a valuable adjunct in the treatment of this particular group of patients. By employing sympathectomy as a preliminary procedure it has been possible in some instances to avoid transmetatarsal amputation. We have been gratified to observe that following sympathectomy in many of these patients with localized gangrenous processes, such as those shown in some of Doctor McKittrick's slides, sufficient improvement in the circulation may take place for the process to be arrested with complete healing and with a minimal loss of tissue, thus precluding the necessity of subsequent amputation, either at the transmetatarsal level or higher. In a series of 32 cases of this kind treated in this manner and followed from six months to four years, amputation was completely avoided in 50 per cent.

DR REGINALD H. SMITHWICK, Boston, Mass. As Doctor McKittrick and his associates have indicated, the advent of chemotherapy and antibiotics have made it possible to consider conservative amputations in increasing numbers of patients. The degree of success which they have had is most impressive to me, and should stimulate a widespread interest in reducing the number of major amputations which are being performed in the presence of localized ulceration and gangrene in patients with peripheral vascular disease.

Valuable as chemotherapeutic agents and antibiotics may be, other factors also are of great importance in determining the outcome of conservative amputations of toes or portions of the foot, particularly when extensive main vessel obliteration is present.

The first essential is that the collateral circulation be adequate for healing. There is no absolutely certain way to determine this, but I have found the following simple rules of thumb to be quite reliable. First, if the temperature of the skin at the site of amputation is 75 degrees Fahrenheit or more after exposure of the extremities to a room temperature of 68 degrees Fahrenheit for one hour, one can be reasonably certain that an adequate blood flow exists. Secondly, when, after blanching of the foot on elevation, flushing in the dependent position begins in twenty seconds or less, in all probability the collateral circulation is adequate. If evidence of an active vasoconstrictor mechanism is detected by appropriate studies, it is advisable to sympathectomize the extremity as a preliminary measure.

If adequate circulation seems to be present, one then comes to the actual operative procedure. Particularly when one is contemplating a closed amputation, the preparation of the operative field is of great importance. This requires a very careful walling off of the ulcerating or gangrenous areas, with meticulous preparation of the skin with soap and water, using cotton or some non-traumatizing substance for this purpose. Recent experiences with Phisoderm and G-11 suggest that this may be of great value in the preparation of the skin. This is a most important part of the operation, and should be done by the surgeon himself.

The actual technic of amputation is of great importance. The skin flaps must be fashioned without trauma or handling of the tissues with toothed forceps or other irritating instruments. No unnecessary undercutting of flaps is permissible. There must be no dead space. The skin must be approximated without tension, placing the sutures so as to obtain perfect approximation without gaping of fat between them, and tied so as not to obstruct the circulation. The margin between success and failure may be very slight, and for this reason I wish to emphasize these fundamental points, because I know from experience that unless they are more fully appreciated the percentage of success will be low.

In addition to transmetatarsal amputations, at times one may consider the amputation of a single toe either through the proximal phalanx or the metatarsal level. If the remaining toes are rigid and the circulation questionable, the transmetatarsal procedure is preferable. These amputations may be carried out through any portion of the metatarsal bones, and more recently I have found that a very useful foot results from amputations through the distal portion of the tarsal bones. In general, I make the skin flaps where I feel the circulation is adequate, and section the bone at whatever level is necessary to insure perfect approximation of the flaps.

I feel that Doctor McKittick and his associates are to be congratulated on this excellent presentation.

DR LELAND S MCKITTRICK, Boston, Mass. I want to thank the discussers for adding and contributing so much to this discussion because all of the points brought out are very important. Doctor Smithwick and Doctor Herrmann brought out the fact that technic cannot be over-emphasized. The operation must be carefully done, with great attention to detail, or, as Doctor Smithwick has pointed out, the results will not be good.

We have not tried the skin graft. That is a fascinating approach. We have closed them all, except those wherein we delayed closure. We disregard the tendons. We close the skin with the greatest of care, using fine wire sutures. We have used this on both diabetics and non-diabetics, in reply to Doctor DeBakey's question, but most of our patients have been diabetics.

We have used sympathectomy in a limited number of patients. We feel that there is a group, just as Doctor DeBakey has pointed out, for whom sympathectomy may be the means of avoiding operation, or of adding to the security of amputation. In that patient with the defect shown on the slide, who had had a previous sympathectomy, closure might not have succeeded had it not been used.

I would like to re-emphasize one point. Doctor Smithwick has said that the margin of safety is small. Whether the procedure succeeds or fails in this group with borderline circulation will depend upon the care and preparation of the patient, the judgment and selection of the proper time to do the operation, and the care with which the technic is carried out. The selection of the proper time for this operation probably is the most important single factor in its success.

RECURRENCE OF GASTRIC ULCER AFTER COMPLETE VAGOTOMY*

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DIVISION OF THE VAGUS NERVE supply to the stomach has been performed on 521 patients at The University of Chicago Clinics during the six year period from January, 1943, to January, 1949. In only 20 patients was the operation done for the treatment of gastric ulcer. Because the chief problem in gastric ulcer is the possibility of cancer, subtotal resection was performed whenever the lesion would permit its removal with a sufficient margin of normal tissue to have some significance as a therapeutic measure, should subsequent microscopic study show the presence of carcinoma. Total gastrectomy was not considered wise in the absence of proved cancer. Vagotomy was thus a substitute for a partial gastrectomy which would either not remove the lesion at all or be inadequate in the presence of carcinoma. A number refused gastrectomy altogether but were willing to have the less mutilating vagotomy. A report of the first eight patients was made two years ago¹ and the problem is now reconsidered because subsequent experience has produced some modifications in our views. It is now clear that vagotomy is not as effective in gastric ulcers as we have found it to be in duodenal and gastrojejunal ulcers. We have not yet encountered a duodenal ulcer that has failed to heal or has recurred when the vagotomy has been complete as determined by repeated physiological tests. Failures have been observed, but these have all occurred after incomplete vagotomy in patients where a positive gastric secretory response to insulin hypoglycemia has been obtained on repeated testing, and the nocturnal hypersecretion has not been reduced.

Of the group of 20 patients with gastric ulcers, 17 had vagotomy alone, two vagotomy plus gastroenterostomy, and one vagotomy plus partial gastrectomy. At the present time 11 of these patients are entirely free of symptoms on an unrestricted diet and without medication. One died at home two months after operation, of a cerebral hemorrhage, autopsy was not secured, so the status of the ulcer is undetermined. One patient died of a brain tumor five months after operation. Autopsy in this case revealed that the gastric ulcer had healed. One patient had a vagotomy plus a wedge resection of the ulcer on the lesser curvature. Gastroenterostomy was subsequently performed because of obstructive symptoms, and the patient died from a transfusion

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reaction due to mis-matched blood. In one patient the diagnosis of a gastric ulcer on the lesser curvature was based on roentgenogram findings. Vagotomy was performed, although at the time the surgeon could not be certain of the presence of an ulcer. Symptoms persisted, together with positive roentgen ray findings, and 19 months later a sub-total gastrectomy was performed. No ulcer was found in the resected specimen, and inspection of the short cardiac segment also failed to disclose an ulcer. Persistence of symptoms after the resection indicates that the original diagnosis was in error, and that the patient never had an ulcer. One patient had a severe hemorrhage from a large gastric ulcer on the lesser curvature six weeks after vagotomy. The ulcer was later excised and the patient is well at the present time. Four patients continued to have ulcer distress 4 months, 5½ months, 13 months and 22 months after vagotomy. The first three of these patients submitted to sub-total gastrectomy, and in each case an unhealed gastric ulcer was found in the resected specimen.

It is thus apparent that in at least five of the 20 patients with gastric ulcers, vagotomy failed to bring about the symptomatic relief and objective evidence of healing usually observed following this operation in duodenal and gastrojejunal lesions. In three of the five patients the vagotomy was complete as evidenced by persistently negative responses to insulin hypoglycemia, together with a satisfactory reduction in the output of acid from the fasting stomach. Summaries of these cases follow.

A N, a 66-year-old housewife, was hospitalized in October 1947 with the complaint of typical abdominal distress for the previous four months. She had had one tarry stool three months previously and had had some episodes of vomiting but no hematemesis. There had been a progressive anorexia with a 30-pound weight loss. In September, 1947, roentgenograms revealed a very large penetrating ulcer on the lesser curvature of the proximal third of the body of the stomach. This measured approximately 2½ cm in diameter. Nocturnal secretion measured 415 cc, with a free acid of 36 clinical units. On October 17, 1947, exploratory laparotomy was performed and a large penetrating ulcer adherent to the liver was found on the lesser curvature of the stomach near the cardia. An abdominal vagotomy was performed. She made an uneventful recovery and was discharged on the twelfth postoperative day. She was readmitted on November 30, 1947, because of recurrent hematemesis during the previous two weeks, so that she became progressively weak, and had anorexia and recurrent severe vomiting episodes. On the day of admission she was exsanguinated and in a state of impending shock. Supportive measures were instituted, but the hemorrhage persisted intermittently, and on the ninth of December the abdomen was reopened and the ulcer excised locally. The patient recovered, following a stormy postoperative course, and was discharged from the hospital on January 16, 1948. On January 4, 1948, gastric secretory studies were made, and a night secretion varying from 420 to 750 cc, with 25 to 57 units of free acid was obtained, this despite the fact that there was a large food residue. The insulin test was also interpreted as being probably positive. Roentgen ray examination in January, 1948, revealed a marked deformity of the mid-portion of the stomach with a narrow channel connecting the two portions, and there was marked gastric retention. The patient's subsequent course has been remarkably uneventful. She has gained 27 pounds to February, 1949, and was eating everything without distress. Further roentgen ray examination of the stomach has not been made.

T B, a 50-year-old salesman, was admitted on January 23, 1947, complaining of typical ulcer distress of three years' duration. He had vomited frequently, and for the past month the pain had been very severe, especially at night. Two years previously he had an episode of tarry stools. Roentgen ray examination in December, 1946, showed a large ulcer crater in a deformed duodenal bulb without obstruction. Roentgenogram of the gallbladder revealed stones. On January 25, 1947, his night secretion was 2440 cc with a free acidity of 39 clinical units and a total acid output of 95 milliequivalents. On January 27, 1947, vagotomy and cholecystectomy were performed under spinal anesthesia. The ulcer was found to be on the gastric side of the pylorus. Three weeks after operation the patient had recurrence of ulcer distress accompanied by vomiting. Roentgen ray examination on February 19, 1947, showed persistence of the crater in the pyloric canal, but it was smaller in size. Distress persisted, and on March 11, 1947, roentgen ray examination showed that the crater was still present. On March 27, 1947, the night secretion was 840 cc with no free acid, and on May 13, 1947, 650 cc with no free acid. Two insulin tests were negative. On May 16, 1947, a sub-total gastrectomy was performed. Examination revealed the resected ulcer to be located just on the gastric side of the pylorus on the lesser curvature (Fig 1). Microscopically it was benign. Eight months after operation he was relieved of ulcer distress but could not eat fatty foods and had lost about eight pounds in weight. When last seen in December, 1948, he had no ulcer pain, but complained of moderate diarrhea.

W H R, a 32-year-old farmer, first came to the clinic on May 7, 1948. He gave a history of epigastric distress and pain under the lower sternum beginning in November, 1941, and persisting with temporary intermissions to the time of admission. The pain was usually constant, but was relieved by the ingestion of food and alkalies. One episode of severe hematemesis with associated tarry stools occurred in 1941, requiring repeated transfusions. Roentgen ray examination revealed an ulcer in the stomach. There were no further episodes of bleeding, but the epigastric distress persisted in spite of a fairly accurate medical management. Fluoroscopic examination on May 8, 1948, failed to reveal a lesion in the stomach or duodenum. The night secretion averaged 550 cc with no free acid. A laparotomy was performed on May 10, 1948, and the abdomen was carefully explored without finding any evidence of disease. The stomach and duodenum appeared normal throughout, and there were no scars or adhesions present. The pylorus was patent. The stomach was not opened, but in view of the previous episodes of hemorrhage with symptomatology of peptic ulcer, a vagotomy was performed. Convalescence was complicated by more than the usual amount of gastric stasis, although there was complete relief of the former epigastric distress. Fluoroscopic examination on August 2, 1948, showed marked gastric stasis but there was no evidence of an organic lesion in the stomach or duodenum. The nocturnal gastric secretion on October 31, 1948, averaged 330 cc in a 12-hour period, with no free acid and 27 clinical units of total acidity. The insulin test was negative. Recurrence of epigastric distress similar to that experienced before the vagotomy was noted in October, 1948, and this rapidly became more severe. Gastroscopic examination on October 30, 1948, revealed an ulcer interpreted as benign on the anterior wall of the mid-portion of the body of the stomach. Fluoroscopic examination on November 2, 1948, revealed a gastric ulcer with a crater, demonstrated by a niche 25 mm in length, along the midportion of the lesser curvature of the stomach. A second gastroscopic examination on November 1, 1948, again revealed a large benign ulcer on the anterior wall near the lesser curvature in the mid-portion of the stomach. On November 3, 1948, a sub-total gastric resection was performed. The resected specimen revealed a large, typical, benign gastric ulcer on the posterior wall of the stomach near the lesser curvature (Fig 2). The ulcer crater measured 1.5 cm in length by 7 mm in width and 5 mm deep. The wall surrounding the ulcer was thickened and the mucosa granular. Microscopically there was marked infiltration of the mucosa with round cells, including plasma cells, and

FIG 1



FIG 2

FIG 1—Photograph of resected stomach showing benign pre-pyloric ulcer four months after vagotomy with negative insulin tests afterward
FIG 2—Photograph of resected stomach showing benign gastric ulcer five and one-half months after complete vagotomy

near the muscularis mucosa there were numerous large reactive lymphoid nodules. The sub-mucosa was fibrotic and invaded by lymphocytes, plasma cells, and eosinophils. The serosa, however, and the mesogastrium, were thickened and hyperemic, and the fatty tissue somewhat fibrotic. The ulcer had penetrated the main muscle coats and undercut the gastric mucosa, particularly on its distal border. Its surface was made up of exudate. Immediately under this region was quite dense granulation tissue with focal fibrinoid degeneration. Recovery from the partial gastrectomy was uneventful, and when last seen on April 4, 1949, the patient was feeling quite well, working every day, and was without epigastric distress or diarrhea. He complained of moderate feelings of fullness and distention after eating.

P. B., a 64-year-old physician, gave a history of intermittent gastric pain and distress for 14 years, with roentgenogram demonstrating a duodenal ulcer on several occasions. There had been one episode of hematemesis in 1933, and he had had recent night pain. The patient brought outside roentgenograms which demonstrated a healed duodenal ulcer and a new ulcer crater on the lesser curvature of the stomach, according to the history this crater had originally been seen in 1939. There was no history of obstruction or co-existent disease. Medical management had been good. Laparotomy on November 24, 1947, showed a scar and an adhesion of the old ulcer in the first portion of the duodenum. There was no evidence of obstruction. On the lesser curvature of the stomach on the mid-section was an indurated area with a perforating ulcer whose crater could be felt. A subdiaphragmatic vagotomy was performed. Postoperatively there was a temperature elevation of 38 to 39 degrees rectally for two days which may have been due to a mild atelectasis. A six-week follow-up showed moderate diarrhea, decreasing in severity since the time of operation. There was no ulcer distress but there were mild symptoms of stasis. The patient's weight gain progressed to 26 pounds in November, 1948, when, for the first time, ulcer distress recurred. An insulin test was negative seven months postoperatively but was positive on December 14, 1948, nocturnal secretion was of low volume with no free acidity. Roentgen ray revealed a lesser curvature gastric ulcer and a sub-total gastrectomy was performed on December 15, 1948. A benign ulcer, recurrent at a previously involved site, was found on pathologic examination of the specimen. In January, 1949, the patient was making a favorable convalescence without ulcer distress.

H. A., a 46-year-old machinist, was admitted to the clinic complaining of typical ulcer distress for the previous eight years. He had had no night pain, no hemorrhages, no perforation, and no obstructive symptoms. Medical management had been excellent and had included a course of roentgen ray therapy to the fundus of the stomach. Repeated roentgen ray examinations since 1942 had demonstrated a recurring, benign, gastric ulcer with hour-glass deformity of the stomach. On November 22, 1946, the night secretion was 861 cc., with no free acid, and the insulin test was positive. On December 4, 1946, a transabdominal vagotomy was performed under spinal anesthesia. A firm, freely movable mass could be felt high on the lesser curvature of the stomach. On December 12, 1946, one insulin test was negative. Gastroscopy on July 2, 1947, showed considerable gastric retention and a possible superficial ulcer. In October, 1947, he complained of recurrent epigastric distress which was considered to be ulcer distress. Roentgen ray examination on November 5, 1947, revealed an hour-glass contraction but no definite crater. Eighteen months postoperatively he continued to have pains similar to his preoperative distress. Roentgenogram on June 23, 1948, revealed persistent deformity of the greater curvature of the stomach with no evidence of a crater.

The development of benign gastric ulcer in patients who have previously had a vagotomy for duodenal ulcer with subsequent healing presents an interesting phenomenon. We have had one proved case of this type and there is possibly a second as yet unconfirmed.

The first patient to have a complete vagotomy in this clinic, W B, a white male, age 51 years, had been operated upon in 1930 for a perforated peptic ulcer. He felt well until 1938, when he developed epigastric pain which was most severe two hours after the noon meal and at 2 00 A M. This pain was relieved by food, alkalis, rest, or vomiting. Fluoroscopic examination on December 8, 1942, revealed high grade pyloric stenosis with a large ulcer crater. Nocturnal gastric secretion averaged 1160 cc with a free acidity of 65 clinical units, and a total hydrochloric acid output of 75.4 milliequivalents. On January 18, 1943, a transthoracic vagotomy with resection of 3 cm of both vagus nerves was performed. The ulcer distress promptly disappeared and the nocturnal gastric secretion was reduced to 310 cc with a free acidity of 58 clinical units and a hydrochloric acid output of 18 milliequivalents. There was evidence of marked stasis of food in the stomach, but the patient continued free from distress and in good general condition for about four years. In 1947, typical ulcer distress recurred and gastroscopy revealed a large ulcer on the posterior wall of the stomach near the lesser curvature. The insulin test was repeatedly



FIG 3—Photograph of resected stomach showing gastric ulcer penetrating into the pancreas which developed four years after complete vagotomy for duodenal ulcer. Duodenal ulcer remained healed.

negative and the nocturnal gastric secretion averaged 620 cc with no free acid. A carcinoma was suspected and a sub-total gastrectomy was performed April 11, 1947. The resected specimen disclosed a large benign gastric ulcer (Fig 3) with marked intimal proliferation and thrombosis in the blood vessels in the neighboring gastric wall (Figs 4 and 5).

Of a total of nine patients in our series with both gastric and duodenal ulcers five had vagotomy alone and four vagotomy plus gastroenterostomy. One patient has been lost to follow-up and six are free of symptoms at the present time. One died of intra-cranial hemorrhage six weeks after the vagotomy and at autopsy the duodenal ulcer was healed, the gastric ulcer partially healed. One patient died in the immediate postoperative period of

FIG 4

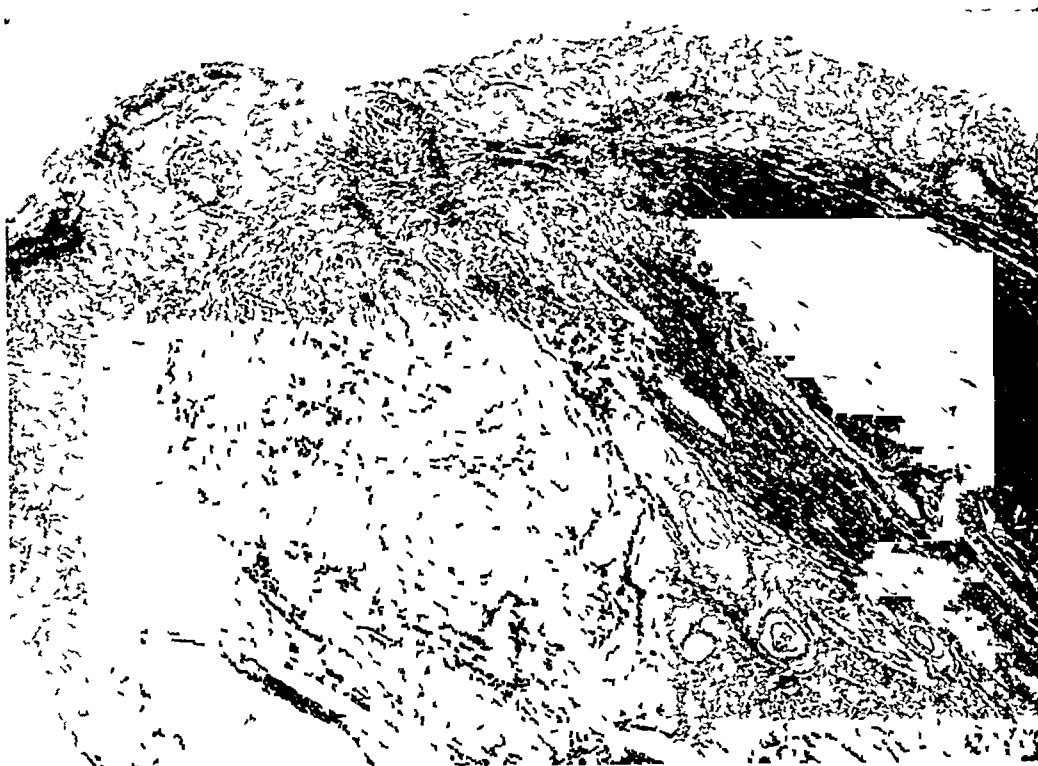


FIG 5

FIG 4—Photomicrograph showing intimal proliferation, thrombosis, and re-canalization in vessels in gastric wall near the ulcer seen in Figure 3

FIG 5—Higher magnification showing details of thrombosis, organization, and re-canalization of vessels in Figure 4

persistent bleeding from the gastric ulcer. This history is summarized as follows:

R. W., a 65-year-old white male, was admitted to the clinic on July 11, 1947, complaining of typical ulcer distress for the previous 30 years. Medical management had been inadequate. He was in profound alkalosis as a result of persistent vomiting when he came to the hospital. Fluoroscopic examination revealed high-grade pyloric obstruction with marked gastric retention. On July 20, 1947, following hematemesis and melena, the patient went into vascular collapse necessitating repeated transfusions. On July 22, 1947, he was transferred to surgery, where supportive therapy was continued, and the patient received 3 more transfusions. Although still in a precarious state and with moderate alkalosis, on July 24, 1947, a laparotomy was performed. Exploration of the stomach revealed a crater on the lesser curvature, 3 cm. from the esophagus, and a duodenal ulcer with obstruction. A vagotomy and posterior gastroenterostomy were performed. The postoperative course was stormy with persistent high fever, and the blood pressure frequently fell to shock levels, and the patient required oxygen. On July 29, 1947, he had a massive internal hemorrhage, and five blood transfusions were given. The blood pressure stabilized on the following day, but then he had another massive hemorrhage, and accordingly, on July 30, 1947, he was re-explored. The stomach was opened and found to be filled with a large blood clot which, when removed, revealed a large shallow ulcer crater on the lesser curvature. In the center of the ulcer an arteriosclerotic artery was seen spurting blood. This was ligated with a mattress suture and the abdomen closed. The patient's condition failed to improve in spite of repeated transfusions and other supportive measures. Aspiration pneumonia developed, and death occurred on August 13, 1947.

TABLE I—*Average Twelve-Hour Night Gastric Secretion in the Empty Stomach of Normal Individuals and Peptic Ulcer Patients*

	Number of Cases	Volume in CC	Free Acid in Clinical Units	HCl Output in Milli- equivalents
Normals	33	581	31	18
Normals (prison)	23	621	44	30
Duodenal ulcers before vagotomy	135	1 085	52	60
Duodenal ulcers after vagotomy	70	521	22	11
Gastric and duodenal ulcers before vagotomy	8	1,106	38	42
Gastric and duodenal ulcers after vagotomy	8	459	12	5.5
Gastric ulcers before vagotomy	14	773	23	17.8
Gastric ulcers after vagotomy	10	465	3	1.4

In our previous report¹ we commented on the fact that hypersecretion of gastric juice was not found in patients with gastric ulcer, although this was the usual finding in duodenal ulcer. Subsequent experience has confirmed this observation, and is well illustrated in Table I, which displays the volume, free acidity, and total acid output in the nocturnal secretion of patients with various types of peptic ulcer compared with normal individuals. It is probable that the most significant figures are those in the fifth column, recording the total output of hydrochloric acid in the empty stomach in a 12-hour period. This figure is obtained by multiplying the volume of secretion in liters by the concentration of hydrochloric acid in clinical units. The product represents the 12-hour output of hydrochloric acid in milliequivalents. The volume and free acid concentration are of lesser meaning, since there is usually

contamination of the parietal secretion by saliva or regurgitated duodenal content

Thirty-three normal individuals secreted an average of 18 milliequivalents of hydrochloric acid, and 14 gastric ulcer patients 17.8, or almost an identical amount. In contrast to this, 135 patients with duodenal ulcers secreted 60 milliequivalents, or three times the normal value. Eight patients with both gastric and duodenal ulcers secreted 42 milliequivalents of hydrochloric acid. In the duodenal ulcer patients the nocturnal acid secretion was reduced to 11 milliequivalents by vagotomy, or less than the normal level, and in the gastric ulcers the secretion of acid was almost abolished. In the patients with both gastric and duodenal ulcers there was also a marked reduction in acid secretion to 5.5 milliequivalents.

Several recent authors^{2, 3} have called attention to striking differences in gastric and duodenal ulcers with respect to total incidence, sex incidence, response to therapy, and other factors. Surgeons have been impressed with the fact that whereas gastrojejunal ulcers frequently were seen following gastroenterostomy or small gastric resections for duodenal ulcer, they were almost never seen when similar operations were done for gastric ulcer. Differences have now been demonstrated in gastric secretion and in the response of these lesions to complete vagotomy. Can these observations be harmonized with the experimental studies on the pathogenesis of ulcer?

The capacity of pure gastric juice to erode the normal mucosa of the stomach and intestines and thus produce a progressive peptic ulcer has been amply demonstrated by controlled experiments in laboratory animals.⁴ Ulcers do not appear under normal conditions because the gastric content is made up of not only gastric juice but substances such as food, saliva, pyloric mucus, and duodenal secretions which dilute and buffer the pepsin-hydrochloric acid. These neutralizing factors constitute a local protective mechanism against ulcer formation which is usually adequate. Removal of the duodenal secretions from the upper intestinal tract reduces the efficiency of this protective mechanism, and when this is done in experimental animals as in the method of Mann and Williamson,⁵ ulcers regularly are produced. A defect of this type has been demonstrated to occur only rarely in man⁶ and probably plays a small role in the clinical problem of ulcer disease. A decreased production of gastric mucus, which comes chiefly from the antrum, has been sought for in ulcer patients, and while some suggestive findings have been reported no definite conclusions can be made. On the other hand, an increase in the corrosive properties of the gastric content due to hypersecretion of gastric juice in response to the physiologic stimulus of food, and more importantly in the empty stomach as well, has been demonstrated in the great majority of duodenal ulcer patients. An excessive nocturnal secretion in these cases has been almost invariably present in our experience.^{7, 8} Both the hypersecretion of the empty stomach and the exaggerated response to food intake have been abolished by complete removal of the vagus innervation of the stomach,

indicating that they are of neurogenic origin. Usually, relief of ulcer distress and objective evidence of healing have paralleled the decrease in acid in the gastric content, and both may be ascribed to this effect.

In gastric ulcer, however, a hypersecretion of gastric juice has not been found, and as a consequence the corrosive properties of the gastric content due to the concentration of hydrochloric acid and pepsin are not greater than in normal individuals. This would suggest that these ulcers are due to a local loss of resistance to gastric digestion, which may in some cases be vascular thrombosis, as called for in the theory of Virchow and Hanser and exemplified in case W B in this report.

We cannot conclude that digestion of the gastric wall by pepsin-hydrochloric acid plays no role in the genesis of gastric ulcers, since as W L Palmer⁹ has repeatedly pointed out, acid is always present in these cases if carefully looked for, and medical management with antacid therapy cures many of them. Also it should be pointed out that most of the gastric ulcers in our series healed following vagotomy, and that this healing was usually accompanied by a marked reduction or abolition of free acid in the night secretion.

The concept of a primary difference in pathogenesis between gastric and duodenal ulcers may be useful in directing therapy. Hypersecretion with resultant increase in the corrosive properties of the gastric content in duodenal ulcers calls for measures to reduce the hypersecretion. Since this hypersecretion is neurogenic in origin, vagotomy appears to be the logical procedure. Vagotomy is clearly less indicated in gastric ulcers, since hypersecretion is not present, and in any case the possibility of cancer dictates a partial gastrectomy whenever practicable.

Gastrojejunal ulcer clearly belongs with duodenal ulcer in pathogenesis. Here a previously normal area of jejunal mucosa succumbs when exposed to the digestant action of the gastric content. It is not digested away by the normal content, as is evidenced by the absence of stoma ulcers when gastroenterostomy is done for gastric ulcers or pyloric cancers, or when performed in normal dogs. Stoma ulcers are commonly found following gastroenterostomy in duodenal ulcer patients with excessive nocturnal secretion. The fact that antrum resection does not prevent gastrojejunal ulcers is further evidence that nervous factors are more important in these lesions, and this conclusion is borne out by the favorable response of these ulcers to vagotomy.

A deleterious effect of gastric stasis is indicated in this study. The patient who developed a gastric ulcer four years after vagotomy for duodenal ulcer had persistent severe retention. Although he had a stenosing duodenal ulcer, a supplementary gastroenterostomy was not performed because the vagotomy was done by the transthoracic approach and at that stage in our study it was considered essential to determine the effect of the vagotomy alone. Two of the patients with gastric ulcers that failed to heal following vagotomy had persistent gastric stasis. A supplementary gastroenterostomy was not usually

done in patients with gastric ulcers because this was thought to be unwise in the absence of organic obstruction

While the major cause of gastric stasis following vagotomy is undoubtedly the marked reduction in the tonus and motility of the body of the stomach following the procedure, an important factor in many cases is pylorospasm of varying degree. This is indicated by the fact that when gastroenterostomy was performed in addition to vagotomy in 262 patients in our series, retention in the immediate postoperative period was less and resumption of normal emptying occurred sooner than in those with vagotomy alone. Since we are now persuaded that vagotomy protects against the development of gastrojejunal ulcer, posterior gastroenterostomy has been adopted as a routine procedure when vagotomy is performed for duodenal ulcer. It is quite possible that had gastroenterostomy been done in addition to vagotomy in the gastric ulcers in this series, the results might have been better.

In a recent report¹⁰ Finsterer gives an account of 614 operations he has performed on ulcers in the region of the cardia. In 79 of these, the ulcer was left in situ and the lower half of the stomach removed after the method of Kelling and Madlener. The operative mortality was 5 per cent, and about 90 per cent of the patients remained free of pain. The beneficial effect of this operation probably depends on the reduction in gastric secretion secured through removal of the antrum. In a series of experimental studies, my associates E. R. Woodward and R. R. Bigelow, and I have recently determined that of the total gastric juice produced in dogs, roughly 40 per cent is secreted in response to vagal stimuli, 40 per cent from the stimulation from the antrum, and 20 per cent from the intestines. It is accordingly probable that vagotomy produces just as great a reduction in gastric secretion in gastric ulcer patients as would be secured by the Kelling-Madlener operation, and if combined with a gastroenterostomy to control the factor of pylorospasm, would accomplish just as much by a more conservative operation.

CONCLUSIONS

1 In a group of 17 patients with gastric ulcers treated by vagotomy alone, the ulcer failed to heal or recurred in five or 29 per cent. In three of these the vagotomy was complete.

2 In a group of 197 patients with duodenal ulcers treated by vagotomy alone, gastric ulcers subsequently developed in two, although the vagotomy was complete and the nocturnal hypersecretion abolished in both instances.

3 In a group of 262 patients with duodenal ulcers treated by vagotomy and gastroenterostomy, no gastric ulcers have so far appeared.

4 In patients with duodenal ulcers, and in those with co-existing duodenal and gastric ulcers, the output of hydrochloric acid in the nocturnal fasting secretion is from three to four times the amount in normal individuals.

5 In patients with gastric ulcers the output of hydrochloric acid in the nocturnal fasting secretion is the same or less than that in normal people.

6 Complete vagotomy produces a much greater decrease in the output of hydrochloric acid in duodenal than in gastric ulcers (a ratio of 49 to 16.4 miliequivalents)

7 The absence of gastrojejunal ulcers following partial gastrectomy or gastroenterostomy for gastric ulcer or pyloric cancer in man or following gastroenterostomy in dogs indicates that the jejunal mucosa can resist the digestant action of the gastric content when the secretion of gastric juice is within the normal range, or depressed

8 The frequent occurrence of stoma ulcers following gastroenterostomy or antrum resection for duodenal ulcers indicates that the jejunal mucosa cannot resist the digestant action of the gastric content when hypersecretion exists, and furthermore, that this hypersecretion is not abolished by removal of the antrum

9 The healing of duodenal ulcers following vagotomy and the absence of gastrojejunal ulcers following combined vagotomy and gastroenterostomy, indicates that both of these ulcers are due to the increased corrosive properties of the gastric content as a result of hypersecretion

10 The absence of hypersecretion in gastric ulcers suggests that these lesions are not due to an increase in the corrosive properties of the gastric content but rather to a decrease in resistance on the part of the gastric wall

11 Vagotomy is not indicated in the treatment of gastric ulcers because hypersecretion of neurogenic origin is not present, and because sub-total gastrectomy may accomplish something in the way of therapy should the lesion prove to be cancerous

12 For juxta-esophageal ulcers vagotomy and gastroenterostomy will probably accomplish as much as the Kelling-Madlener operation. Total gastrectomy is not warranted in these cases in the absence of proved cancer. Sub-total gastrectomy does not remove these lesions with a sufficient margin to have therapeutic significance should the disease prove cancerous

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Editorial . .

THE PLACE OF RESEARCH IN A SURGICAL TRAINING PROGRAM

IT IS SELF EVIDENT that all surgeons will not be productive investigators. Even among those selected for residencies in teaching hospitals, there are many who will not be of much value to society in this way. The questions arise, therefore, why place so much emphasis on research in the training of young surgeons? Would it not be better to segregate those with an interest and aptitude for research from the others? Would it not be better to detach those who are interested from clinical training for periods of investigation, so that their research activities will not interfere with the smooth functioning of a clinical service?

There is, of course, no one set of answers to these questions. The value of an outstanding contribution to surgical science is so great as to be hard to overestimate. Therefore, those institutions so situated as to be in the forefront of scientific advance are certainly justified in planning their overall programs so as to enhance the probability of successful research as far as possible. They often need their residents to provide the medical manpower required.

Another consideration stems from the fact that much which is published as new and worthwhile is little more than conjecture and opinion. It is obviously important that clinicians who are not investigators themselves, nevertheless develop judgment and skill in evaluating the work of others. Probably nothing gives quite so much insight in this regard as the experience of collaborating in a research project at first hand.

Thus, in teaching hospitals with research facilities, we have two good reasons for expecting men taking surgical training to participate in research activities, first, to provide the man hours to carry forward such work and, second, to give the trainee experience which will strengthen his critical judgment of investigative work.

There are other possible reasons for exposing such a comparatively large group of men to this type of experience. Occasionally an able man without much interest in original work will catch the fire of an older investigator and develop an interest of his own. This is rare in our experience, but it is common for those who have an interest to find it strengthened through use or for it to fade out through disuse. More important is the mind set which one gets toward his clinical work in an institution where everyone is trying to add to the sum total of surgical knowledge, that is, to do more for patients than established methods have accomplished in the past. This is essential in the training of the best clinicians, yet it is derived for the most part from a spirit of investigation.

In those institutions in which almost all surgical trainees are expected to share in the responsibility for the advance of knowledge, the question arises as to how this is best accomplished. Should a man be allowed to concentrate entirely on his clinical work for a stretch of time and then be provided with leisure for full time research, or should he be expected to carry both concurrently? Heavy as the pressure of clinical work may be on the trainee, it is not likely to be less demanding when his training is finished and he is well established as a clinician in his own right. Therefore, it seems to this author that unless a man learns to carry a load of investigative work concurrently with clinical work during his residency, it is not likely that he will get any research done after his training is completed unless he becomes a full time investigator.

On the other hand, if both activities are to be engaged in concurrently, it is essential that the clinical load be shared widely enough so that it does not require all the time and energy of the individual. When the clinical load is permitted to approach this latter level, the ability to make progress with a research problem becomes a function of stamina and work tolerance rather than a function of originality and perspicacity.

The whole question of the place of the clinician in research is one that demands careful consideration. While a period of clinical work may be helpful in the orientation of a full-time laboratory investigator, the major advantage of combining research and clinical training seems to consist in having men with knowledge of and capacity in research methods in day to day contact with the problems of the patient. It should be their special opportunity to recognize significant problems and to pick out those which may be susceptible of solution by the technics made available by full time laboratory investigators.

To the extent that this generalization is true, it would seem that in surgery we should aim, not exclusively, but for the most part, to train investigators who will remain in clinical work. While periods of full-time research often have a place as part of the training program, periods of full time clinical work, from which research is excluded, are not conducive to the training of men who are to continue in investigative work after they become clinicians in their own right. It is of the greatest importance that they form a strong habit of devoting time to the search for new knowledge at the same time that they perform their clinical duties carefully and conscientiously.

JONATHAN E RHOADS



THE CAUSE OF DEATH IN STRANGULATION OBSTRUCTION AN EXPERIMENTAL STUDY

I CLINICAL COURSE, CHEMICAL, BACTERIOLOGIC AND
SPECTROPHOTOMETRIC STUDIES^{*}

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THE MORTALITY IN ACUTE intestinal obstruction has decreased from around 60 per cent at the turn of the century to 10 to 20 per cent in the larger clinics at the present time (Table I) A comparison of different series of cases from the same clinic over the period of years further demonstrates this decline—University of Pennsylvania,^{7, 9, 19} Massachusetts General Hospital,^{3, 4, 10, 16} Johns Hopkins Hospital,^{7, 20} University of Minnesota Hospitals^{14, 18}

This decline in mortality, however, has been manifested more in cases of simple obstruction than in strangulation obstruction^{6, 16, 19} In 1947, Eliason and Welty¹⁹ reported a mortality of only one per cent in those cases of obstruction not complicated by strangulation or carcinoma On the other hand, even as late as 1940, Schlicke, Borgen and Dixon¹⁷ reported a mortality of 56 per cent of those cases where gangrenous bowel was found at operation, and even more recent reports showed a mortality of 20 to 40 per cent in this group of patients^{18, 20} It is of particular interest to note that although at the present time interference with the circulation occurs in only 17 to 33 per cent of the total cases,^{16, 20} the mortality ranges between 25 and 40 per cent, and these cases account for more than half of the total deaths reported in the various series^{16, 18, 20} The continued high mortality in cases of strangulation obstruction indicates that factors other than those amenable to present improved methods of management exist in this condition

We have investigated the problem of strangulation obstruction utilizing certain of the newer concepts of management in an attempt to further clarify the cause of death Following the creation of a strangulated ileal obstruction in dogs, the animals were treated for hemorrhage, shock, dehydration and electrolyte loss, and studies were made on the blood, peritoneal fluid, and gut contents

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METHODS

Seven carefully selected, vaccinated, dewormed adult mongrel dogs weighing between 9.4 and 17.0 Kg were used in this experiment. Following a 24 hour period of starvation, the animals were operated upon under Na pentobarbital (24.0 mg per Kg) anesthesia. Samples of blood for control chemical studies were taken on the day before or the morning of operation. Strict aseptic technic was used throughout. All the omentum distal to the spleen was excised in order to facilitate the withdrawal of peritoneal fluid and to obviate the omentum as a source of revascularization of the strangulated segment.²² At a point between 100 and 150 cm from the ligament of Trietz, the bowel was severed and the cut ends closed by the Parker-Kerr technic (Fig. 1). Fifteen centimeters above the proximal closed end a 30 cm segment of bowel was strangulated by doubly ligating the veins in the base of the mesentery. The communicating arteries and veins at either end of the

TABLE I

Year Reported	Period Covered	Author	Hospital	No of Cases	Mortality %
1888	1880-1883	Fitz ¹	Collected	146	70.0
1900	Up to 1900	Gibson ²	Collected	1000	43.0
1908	1898-1907	Scudder ³	Mass General	121	60.0
1920	1908-1917	Richardson ⁴	Mass General	118	50.0
1921	1912-1921	Finney ⁵	Johns Hopkins	245	36.0
1925	1900-1925	Van Buren and Smith ⁶	Collected	1089	41.8
	1914-1923		Presbyterian	174	58.0
1929	1905-1922	North ⁷	Univ of Pa	200	30.5
1925	Up to 1925	Souttar ⁸	Collected	3064	32.0
1929	1922-1928	Brill ⁹	Univ of Pa	124	36.3
1932	1918-1927	McIver ¹⁰	Mass General	335	31.0
1929	1924-1929	Miller ¹¹	Charity Touro Infr	343	61.0
1934	1922-1932	Christopher and Jennings ¹²	Evanston	127	44.9
1938	Up to 1938	Scudder ¹³	Collected	2150	24.0
1938	1931-1938	Wangenstein ¹⁴	Univ of Minn	156	17.9
1940	1936-1939	Johnston ¹⁵	Wayne Univ	63	19.1
1940	1927-1938	McKittrick and Sarris ¹⁶	Mass General	136	20.0
1940	1938-1939	Schlicke, Barger and Dixon ¹⁷	Mayo Clinic	166	22.0
1943	1938-1942	Dennis and Brown ¹⁸	Univ of Minn	110	15.5
1947	1934-1943	Eliason and Welty ¹⁹	Univ of Pa	292	11.0
1946	1936-1945	Calihan, Kennedy and Blain ²⁰	Johns Hopkins	204	20.0
1946	1943-1945	Moses ²¹	Gallinger Municipal	118	8.0

strangulated segment, running parallel and adjacent to the bowel on the mesenteric border, were severed and doubly ligated. A segment of plastic tubing was threaded through normal bowel into the strangulated segment, two multiperforated latex tubes were placed in the lateral gutters, all tubes were brought out onto the anterior abdominal wall through stab wounds, and the abdomen was closed. At the conclusion of the procedure the strangulated segment was invariably dusky blue in color, and in some cases had begun already to exude a pink serous transudate.

Another segment of plastic tubing was then threaded through the jugular vein into the superior vena cava, anchored to the skin, and then connected to a gravity drip, thus enabling the animal to receive large amounts of fluids constantly while moving freely about in his cage.

Parenteral fluid administration was begun at operation and continued con-

stantly throughout the period of survival, the amount and type of fluid, *i e*, blood, glucose and saline or gelatin, being determined by the hematocrit and hemoglobin at two or four hour intervals and by the clinical condition of the animal. Postoperatively, usually at four hour intervals, the peritoneal cavity and gut were aspirated, and blood samples were withdrawn from the femoral artery for serial studies. In all instances all the peritoneal fluid obtainable from the latex tubes at each interval was removed under sterile conditions. In six of the seven animals, only several cubic centimeters of bowel contents were removed for chemical determinations. In the remaining animal (No 347), the gut contents were evacuated as completely as possible at four hour intervals. Blood and peritoneal fluid cultures were taken at various intervals, and gut contents were cultured just prior to death in a number of the animals.

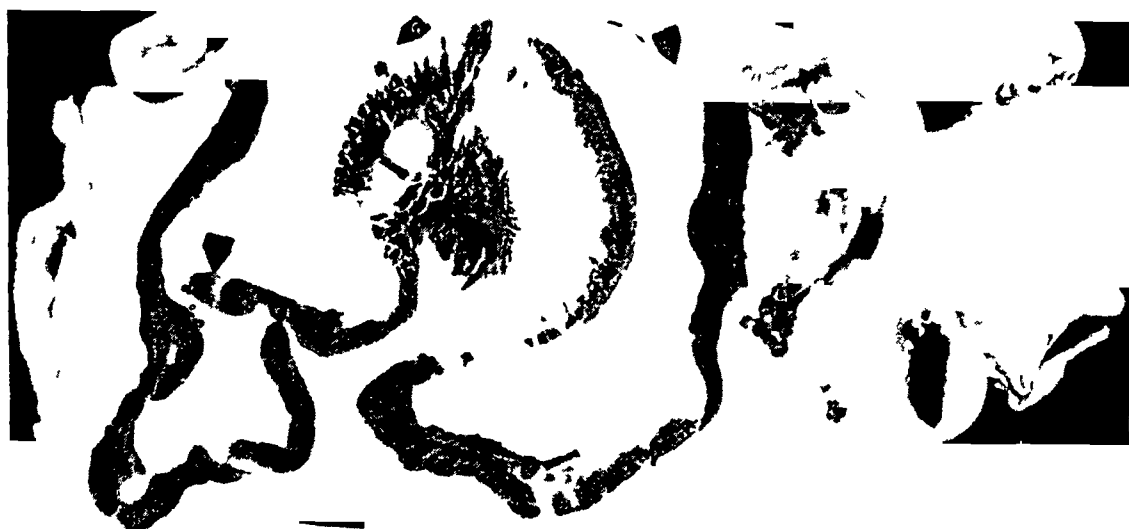


FIG 1—Photograph of strangulated segment of bowel from dog No 331. The distal turned in end was sutured to the side of the proximal closed end in order to prevent intussusception. This was the usual picture noted in five of the seven dogs (see text).

The following chemical determinations were done: specific gravities,²³ proteins,²⁴ urea nitrogen,²⁵ nonprotein nitrogen,²⁶ creatinine,²⁶ uric acid,^{27, 28} total nitrogen,²⁹ amino acid nitrogen,³⁰ amylase,³¹ lipase,³² chlorides,³³ calcium,³⁴ CO₂ combining power,³⁵ pH,³⁶ potassium³⁷ and spectrophotometric studies.^{38†}

* The absorption spectrum curves are plots of *fractional molecular extinction coefficients*, ϵ (at concentration, $C = 1$ mM per liter, and at depth, $d = 1$ cm), against wave-length in μ . ϵ is a negative logarithmic function of the amount of light transmitted by the solution, much the same as pH is the negative log of H^+ , the hydrogen ion concentration, ϵ , not the light transmitted, is proportional to the concentration. Molar concentrations of reference for hemin derivatives refer to the weight containing one iron atom, in the case of hemoglobin the equivalent weight is 16,700, and 1 mM per liter equals 16.7 Gm per liter, or 1.67 Gm per 100 ml. The millimolar concentration has proved convenient and unequivocal for the spectrophotometric notation of the various hemin derivatives.^{38a} Since hemoglobin, hemin and hemochromogen derivatives may be converted respectively to spectroscopically practically identical cyan-methemoglobin,^{38a} hemin dicyanide,^{38b} and hemochromogen monocyanides,^{38b} the cyanide derivatives were used for the quantitation of total hemin pigments in the various samples.

The comparison of the absorption spectrum data upon the peritoneal fluid and gut contents with known hemoglobin derivatives was materially aided by reliable information upon the latter, available from extensive work in the laboratory of one of us (DLD)

CLINICAL COURSE

Six of the seven animals responded in similar manner to the procedure and died between 28 25 and 48 hours after operation, with an average survival



FIG 2



FIG 3

FIG 2—Photograph of the strangulated segment from dog No 365 This segment measured 75.0 cm in length

FIG 3—Photograph of the resected segment of bowel from dog No 295 The strangulated segment measured only 25.0 cm in length and was markedly thickened The sharp line of demarcation is clearly shown

time of 36 hours This represents a definite prolongation of life, for in untreated animals with a similar length of strangulated gut death usually occurs between seven and 24 hours^{39, 40} These dogs exhibited a black, necrotic, gangrenous, nonperforated, elongated, dilated^{39, 40, 47, 49} segment of gut The loops were elongated some 25 to 50 per cent, and the wall was moderately to markedly thinned out (Fig 1), but in no case had perforation occurred There was an extremely sharp line of demarcation above and below the strangulated segment, and we found none of the changes in normal bowel described by Moon and Morgan⁴¹ One of these six animals (No 365) demonstrated a

volvulus at autopsy, with a venous obstruction to the proximal obstructed bowel distal to the segment which had been purposely strangulated. The strangulated segment in this animal measured 75.0 cm in length (Fig. 2). As there was no evidence of leakage at the proximal turned-in end nor at the entrance of the tube into the gut, this animal is included in the series and merely represents a more extensive strangulation.

The seventh animal (No. 295) lived for 75 hours, at which time resection of the strangulated segment was performed. The resected segment was blackish brown in color, extremely thickened, and measured only 25.0 cm in length (Fig. 3).

The peritoneum in all cases revealed mild inflammatory changes and plastic exudate in the region of the loop, but in no case were necrotic areas present. The picture was never that of a bacterial peritonitis.

Postoperatively, the animals remained in relatively good condition, moving freely about in the cage up until one to four hours of death. At this time a striking change occurred. The animals obviously became sicker. Retching and vomiting, which had begun in all cases between eight and 14 hours, consisting of a foul smelling bloody fluid, became severe and constant. This final period was quite similar to that observed by Blain *et al.*⁴⁷ and Blain and Kennedy⁴⁸ in their dogs. Death occurred very suddenly and was preceded by convulsive movements of the extremities and gasping respirations. Femoral arterial pulsations were easily palpable in all cases up until several minutes of death, and the animal did not appear to be in clinical shock. Five of the six animals which died developed a terminal rise in the temperature to 103 to 107.6° F just before death, and three of these were over 105° F.

It may be noted in Table II that the hematocrit and hemoglobin values were well maintained throughout the course of survival, only one animal (No. 347) showing a moderate fall. Large amounts of fluids were required to maintain the animals. The total fluid intake ranged between 3000 and 6700 cc. Administration of whole blood varied from 150 to 720 cc per Kg per 24 hours and of 5 per cent glucose in saline from 100 to 340 cc per Kg per 24 hours. The amount of peritoneal fluid removed over the course of survival varied from 603 to 1573 cc.

A study of the gut contents and peritoneal fluid revealed a constant sequence of events which was borne out by detailed chemical, bacteriologic, and spectrophotometric studies.

Within two to four hours after operation a small amount of reddish-black, odorless, coagulable fluid with a specific gravity between 1.030 and 1.040 and a hemoglobin content similar to that in the blood was aspirated from the strangulated gut lumen. The amount of this fluid entering the lumen was small at first but increased as the damage to the gut wall increased. At around 12 hours this fluid became black in color, noncoagulable, had a foul odor, and the specific gravity fell to between 1.015 and 1.024. From this point on the gross character of the fluid did not change, but the volume markedly increased. This later fluid in the gut lumen has been similarly described in strangulated

closed loops,^{39, 42, 43, 45, 50} in simple strangulation obstruction^{47, 48} and in isolated jejunal loops⁵¹

On the other hand, the peritoneal fluid at two to four hours was pink or strawberry colored, clear, odorless, and had a specific gravity between 1019 and 1027. The physical properties as well as the chemical studies (Table III, Fig 4) revealed that this fluid owed its character to the presence of blood and unchanged hemoglobin and, as shown by Laufman and Method,⁵² apparently was derived early almost entirely from the serosal side of the strangulated gut. This continued to be the type of fluid recovered from the peritoneal

TABLE II—*Intake and output data, hemoglobin and Hematocrit Readings on the Strangulated Animals*

Dog	Length of Survival in Hours	Fluid Change First Noted (Hour)	Intake					
			Blood		Glucose Saline		Gelatin	
			cc /L of S	cc /Kg /24h	cc /L of S	cc /Kg /24h	cc /L of S	cc /Kg /24h
331	42	36	1085	65	5525	340	100	6
237	48	48	660	24	2800	101	340	12
235	32	28	980	72	2425	182	200	15
357	35½	34	695	31	2275	101	100	5
347	30	29	805	38	2200	104	400	19
295	75*		550	15	4500	120	200	5
365	28¼	28	1000	50	2455	125	330	17

Output

Peritoneal Fluid		Gut Contents		Urine and Vomitus		Hematocrit		Hemoglobin	
cc /L of S	cc /Kg /24h	cc /L of S	cc /Kg /24h	cc /L of S	cc /Kg /24h	Initial	Terminal	Initial	Terminal
1080	65	87	5	4040	245	55	57	20	19
603	22	53	2	2450	89	47	54	16	18
1400	106	38	3	1495	113	41	46	14	16
1098	48	47	2	1290	58	39	40	13	14
845	41	535	26	615	29	56	37	19	13
674	18	115	3	2425	65	45	43	15	15
1573	80	247	12	1380	70	52	49	18	16

* This animal never developed the fluid change, and the strangulated segment was resected at 75 hours

cavity for a relatively long period of time. During the early stages this fluid was very abundant but decreased as the process progressed, possibly due to a thrombosis of the serosal vessels⁵² or of the mesenteric veins proximal to the ligature^{22, 49}. At variable stages, corresponding closely with the abrupt change in the clinical condition of the animal, the fluid recovered from the peritoneal cavity changed to a reddish black and later to a black fluid very similar in its physical and chemical characteristics to the bowel contents (Table III) (Fig 4). The death of the animal occurred within one to four hours after the appearance of this fluid in the peritoneal cavity. The animal, which lived for 75 hours and was then reoperated upon, never developed the black fluid either in the gut or in the peritoneal cavity. Undoubtedly some degree of

CAUSE OF DEATH IN STRANGULATION OBSTRUCTION

TABLE III—Studies on the Nitrogenous Substances in the Blood, Peritoneal Fluid and Gut Contents

(All values in mg/100 cc.)																																				
DOG 331							237					235					357					347					293					365				
UN	NPN	URIC ACID	CREAT- ININE	TN	UN	NPN	URIC ACID	CREAT- ININE	TN	UN	NPN	URIC ACID	CREAT- ININE	TN	UN	NPN	URIC ACID	CREAT- ININE	TN	UN	NPN	URIC ACID	CREAT- ININE	TN	UN	NPN	URIC ACID	CREAT- ININE	TN							
CONTROL	18				16	31				13	31	0 51	1 2		49	67	0 73	2 09		27	52	0 89			20	66	0 94	1 89								
4	8				25					13	24	0 70	0 85		27	43	0 56	1 56							19	52	1 85	1 50								
12	19				12					17	37	0 74	1 30		31	56	0 59	1 50																		
20	24				14																															
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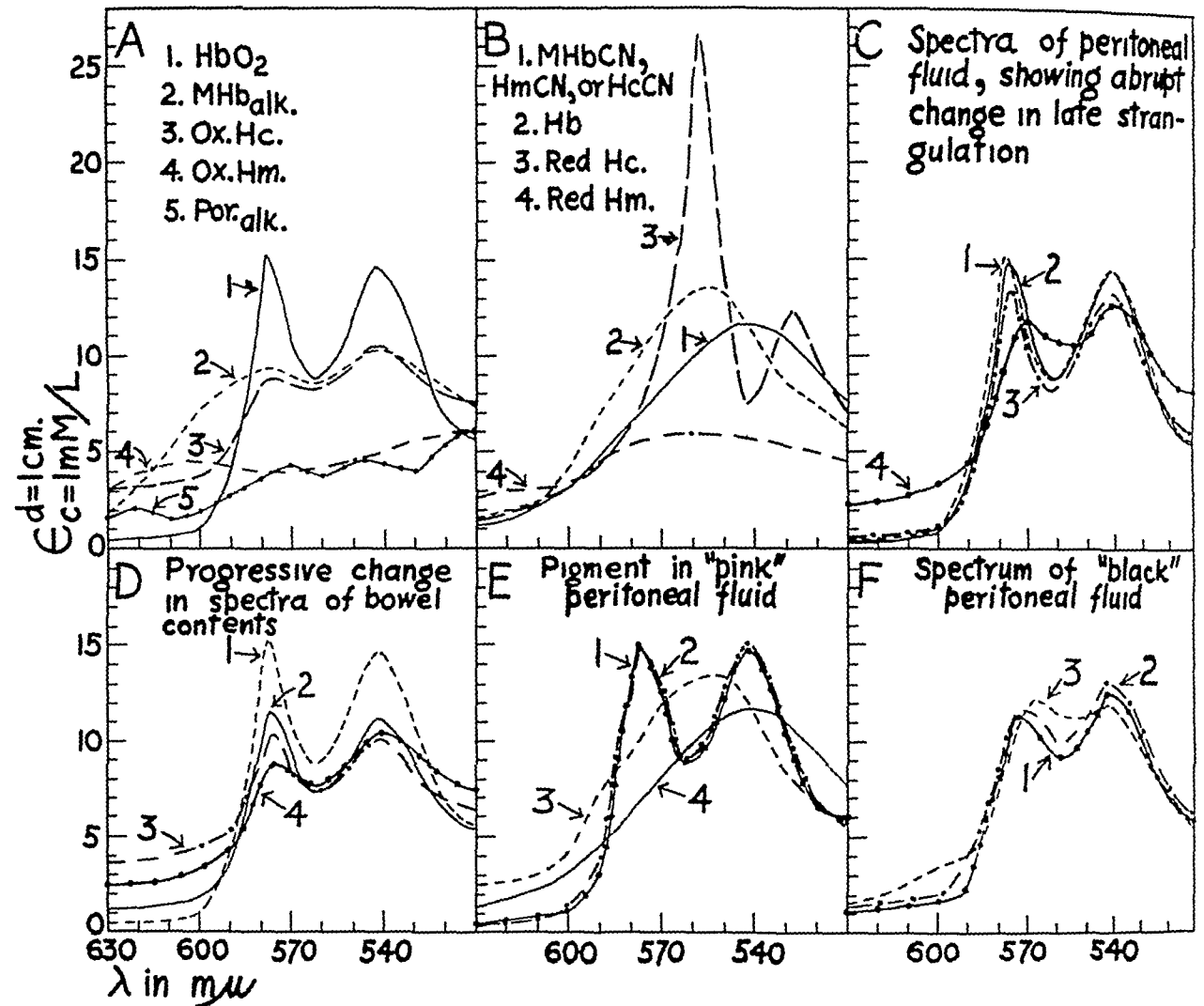


FIG 4

FIG 4—Character and identification of absorption spectrum curves obtained from peritoneal fluid formed after the experimental intestinal strangulation (C, E, and F) and from the contents of the strangulated bowel segment (D). Absorption spectrum curves obtained from blood or derived from the hemoglobin of blood are presented for comparison (A and B).

A—Curve 1, HbO_2 , oxyhemoglobin,⁵⁹ Curve 2, MHb_{alk} , alkaline methemoglobin, pH 9.15,⁶⁰ Curve 3, Ox.Hc , oxidized globin hemochromogen or globanferriprotoporphyrin,⁶¹ Curve 4, Ox.Hm , oxidized hemin or ferrihemin,⁶¹ Curve 5, Por_{alk} , alkaline porphyrin.

B—Curve 1, MHbCN , cyanmethemoglobin,⁵⁹ HmCN , hemin diacyanide,⁶² or HcCN , monocyanide derivative of oxidized globan ferriprotoporphyrin cyanide,^{62, 63} derived respectively from 1 or 2 in A, 4 in A, and 3 in A, Curve 2, Hb , reduced or deoxygenated hemoglobin, derived from 1 or 2 in A by addition of hydrosulfite, $\text{Na}_2\text{S}_2\text{O}_4$, Curve 3, Red Hc (reduced globin hemochromogen or globan ferriprotoporphyrin^{61, 63} derived from 3 in A by addition of $\text{Na}_2\text{S}_2\text{O}_4$, Curve 4, Red Hm (reduced hemin or ferrohemin,⁶¹ derived from 4 in A by addition of $\text{Na}_2\text{S}_2\text{O}_4$).

C—Absorption spectrum curves of peritoneal fluid (from dog No 357) removed at different times following establishment of strangulation obstruction. The curves illustrate the abrupt appearance (reflected in the abrupt change in color from "pink" to black) of the abnormal spectrum, Curve 4. Curve 1, unchanged oxyhemoglobin (same as 1 in A), Curve 2, at 4 hours, original total pigment concentration as MHbCN equals 0.649 Gm per 100 ml, Curve 3, at 32 hours, original total pigment concentration as MHbCN equals 0.387 Gm per 100 ml, Curve 4, at 35 hours, original total pigment concentration as MHbCN equals 1.14 Gm per 100 ml. (Legend continued on opposite page)

revascularization occurred in the strangulated loop of this animal. Microscopically, the mucosal layer was intact whereas in the animals which died varying degrees of destruction were present.

CHEMISTRY

Blood No significant change was noted in the chlorides, calcium^{47, 48} or potassium⁵³. The CO₂ combining power was moderately decreased^{47, 48}. The amylase in the blood was decreased markedly within 12 to 24 hours following anesthesia and operation⁵⁴. Eight hours after strangulation the serum lipase was 10 cc or above in three of the six animals in which studies were made, and in one of the three it was also elevated at death. We have attached much accuracy to our determinations of serum lipase in the dog⁵⁵ and feel these elevations to be significant.

Peritoneal fluid The protein content of the peritoneal fluid was in most instances between 3.4 and 4.5 Gm per 100 cc⁴⁵. The hematocrit of the early peritoneal fluid usually ranged from one up to less than six although in one animal (No. 347) values of 14 to 28 were obtained. No hematocrit readings could be obtained in the reddish black or black peritoneal fluid. The chloride content of the peritoneal fluid was slightly higher than that of the blood, and in two animals peritoneal fluid potassium levels were not elevated⁵³. The amylase in the early peritoneal fluid varied directly with that of the blood.

Nitrogen studies in blood, peritoneal fluid and gut contents We attach no significance to slight variations in the uric acid and creatinine which we obtained (Table III), and in no case did we find values for creatinine as high as those reported by Cooke, Rodenbaugh and Whipple⁵⁶. In all the dogs which died, except the animal with the 750 cm strangulation (No. 365), there was a slight to moderate increase in the blood urea nitrogen³⁹ and blood nonprotein nitrogen^{39, 45, 47, 48}. The increase averaged 65 per cent for the blood urea nitrogen and 55 per cent for the nonprotein nitrogen. In the peritoneal fluid

D—Absorption spectrum curves of contents of strangulated bowel segment (from dog No. 357), showing progressive change at an appreciably earlier time than in the peritoneal fluid (curves in C) toward fluid with the characteristic abnormal spectrum. Curve 1, unchanged oxyhemoglobin (same as 1 in A), curve 2, at 12 hours, original concentration of total pigment as MHbCN equals 9.81 Gm per 100 ml, Curve 3, at 27 hours, original concentration of total pigment as MHbCN equals 2.12 Gm per 100 ml, Curve 4, at 35 hours, original total pigment concentration as MHbCN equals 2.14 Gm per 100 ml.

E—Identification of spectrum of "pink" peritoneal fluid (from dog No. 235) as that of unchanged oxyhemoglobin. Curve 1, at 24 hours, original concentration of total pigments as MHbCN equals 0.432 Gm per 100 ml, pH equals 8.0 (compare with curve 1 in A), Curve 2, obtained after addition of solid cyanide to solution yielding Curve 1 (no change), Curve 3, obtained after addition of solid Na₂S₂O₄ to solution yielding Curve 1 (compare with Curve 2 in B), Curve 4, obtained after addition of ferricyanide (for oxidation) and cyanide to solution yielding Curve 1 (compare with Curve 1 in B). Practically the same curve as 1 was obtained from a specimen removed at 28 hours.

F—Abnormal behavior of pigment in "black" peritoneal fluid (from dog No. 235) towards addition of cyanide or Na₂S₂O₄. Curve 1, at 32 hours, original concentration of total pigment as MHbCN equals 4.46 Gm per 100 ml, pH equals 9.2 (compare with Curve 4 in C and D), Curve 2, obtained after addition of solid cyanide to solution yielding Curve 1 (see the text), Curve 3, obtained after addition of solid Na₂S₂O₄ to solution yielding Curve 1 (see the text).

of the same group of animals the urea nitrogen showed an average increase of 362 per cent and the nonprotein nitrogen of 353 per cent. It will also be noted that this increase was not a gradual one but occurred suddenly during the late stages after the black fluid had appeared. The urea nitrogen and nonprotein nitrogen of the gut contents showed an average increase of 704 per cent and 309 per cent respectively. Here, also, it would seem that a late increase occurred (No 237).

TABLE IV—*Bacteriologic Studies on the Blood, Peritoneal Fluid and Gut Contents*

Dog No	Peritoneal Fluid		Blood	Gut Contents
	Pink	Black or Red Black		
331	Hemo clostridia B coli	Hemo clostridia B coli	Negative throughout	
237	Strep viridans	Non-hemo strep		
	Hemo clostridia	Hemo clostridia	36 h —negative	
	B coli	B coli	48 h —B coli	
	Salmonella	Salmonella	Non-hemo clost	
235	Non hemo strep	Non-hemo clost		
		Non-hemo strep		
	Hemo clostridia	Hemo clostridia	Negative throughout	
	B coli	B coli		
357	Hemo strep	Hemo strep		
	Non hemo strep	Non hemo strep		
	Non-hemo clost	Non hemo clost		
	Hemo clostridia	Hemo clostridia	32 h —Negative	Hemo clostridia
	B coli	B coli	34 h —A aerogenes	B coli
	Hemo strep	Hemo strep	35 h —Hemo clostridia	Hemo strep
	Non hemo strep	Non hemo strep	B coli	Non-hemo strep
347	Non-hemo clost	Non hemo clost	Hemo strep	Non hemo clost
	A aerogenes	A aerogenes	Non hemo strep	A aerogenes
		B proteus	A Aerogenes	B proteus
			B proteus	
295	Hemo clostridia	Hemo clostridia	Negative throughout	Hemo clostridia
	B coli	B coli		B coli
	Non hemo strep	Hemo strep		Non hemo strep
	Non hemo clost	Non-hemo strep		Non hemo clost
	A aerogenes	Non-hemo clost		B proteus
365		B proteus		
	Hemo clostridia	Hemo clostridia	Negative throughout	Hemo clostridia
	B coli	B coli		B coli
	Hemo strep	Hemo strep		Hemo strep
	Non-hemo strep	A aerogenes		Non hemo strep
	A aerogenes			Non hemo clost
				A aerogenes

Bacteriology The peritoneal fluid has been found to be sterile at four to six hours^{43, 57} and even as late as 19 to 20 hours^{47 49}. In general, we found the peritoneal fluid to be sterile up until 14 to 20 hours, at which time the flora of the strangulated gut began to appear, and the late pink peritoneal fluid contained, qualitatively at least, almost identically the same organisms as found

in the red-black or black peritoneal fluid (Table IV) In three of the animals in which the gut contents were cultured just prior to death, the black fluid contained the same organisms as were found in the gut It will be noted, however, that in these cases the same organisms were present in the pink fluid as early as 20 hours In the animal which was resected at 75 hours the peritoneal fluid contained qualitatively the same organisms at 29 hours as were recovered from the resected segment at 75 hours Hemolytic clostridia, *B coli*, and nonhemolytic streptococcus were present in the peritoneal fluid in all cases⁵⁸

Positive blood cultures were obtained just before death in two animals In both cases the black fluid was present in the peritoneal cavity at the time positive cultures were obtained

Spectrophotometric findings In Figure 4, A to F and its accompanying legend, typical results of the spectrophotometric measurements on the peritoneal fluid and bowel contents are presented together with an interpretation of the significance of the spectra The latter is aided by a comparison with absorption spectrum curves obtained from normal hemolyzed blood or derived from the hemoglobin in blood by physical or chemical treatment (A and B, Fig 4) The following points appear to be established unequivocally

- 1 The absorption spectrum of samples of the pink or strawberry colored peritoneal fluid, withdrawn sometimes as late as 32 hours after strangulation, was essentially that of unaltered oxyhemoglobin (E, Fig 4)

- 2 The absorption spectrum of the black peritoneal fluid was markedly and characteristically different from that of oxyhemoglobin and quite identical with the abnormal spectrum of the contents of the strangulated bowel segment Detailed spectrophotometric evidence cannot be presented here, but the findings (in other experiments than those reported in Figure 4) lend themselves to the clear interpretation that the degree of alteration of the spectrum of peritoneal fluid from the character of Curve 2 towards Curve 4 in C depends on the proportion of two components in the mixture, namely, the relative amounts of pink peritoneal fluid and black bowel contents

- 3 In contrast with the abrupt late change in spectroscopic character found in the peritoneal fluid, the alteration towards the abnormal spectrum in the bowel contents was early and progressive (D, Fig 4)

- 4 It may be seen that the abnormal spectra of the bowel contents or of the late peritoneal fluid bear a superficial resemblance to either alkaline methemoglobin (Curve 2 in A), or still more closely to oxidized globin hemochromogen (Curve 3 in A) Both methemoglobin and oxidized hemochromogens should react with cyanide to yield the spectrum typified by cyanmethemoglobin (Curve 1 in B) An examination of the curves in F makes it clear that the abnormal spectrum of the black peritoneal fluid cannot be accounted for by the presence of appreciable amounts of methemoglobin or oxidized hemochromogens, for there was unexpectedly little change after the addition of cyanide (2F) After the addition of $\text{Na}_2\text{S}_2\text{O}_4$ (3F) if methemoglobin were present, a change toward 2B should have been found, or if typical hemo-

chromogens were present in appreciable amounts, a change toward the striking spectrum 3B should have been found

The atypical behavior of the black peritoneal fluid towards cyanide and $\text{Na}_2\text{S}_2\text{O}_4$ suggests that we are dealing with an unusual pigment or pigments. It should be mentioned that most of the pigment in the black bowel contents and black peritoneal fluid were hemoglobin or hemin derivatives since they responded typically to the addition of ferricyanide plus cyanide.

5 To conserve space the spectrophotometric studies upon the blood have not been presented. These demonstrate unequivocally that the abnormal pigment appears in the blood but only very soon after or simultaneously with its appearance in the peritoneal fluid.

DISCUSSION

That shock through the local loss of fluid⁴⁵ may account for death in experimental long loop strangulations is amply demonstrated^{40, 42, 45, 46, 57, 64, 65}. However, even with adequate treatment for shock, life is prolonged but little^{22, 47, 48}. That penicillin when combined with treatment for shock, dehydration, and electrolyte imbalance may prolong life in strangulation obstruction has been shown also and would indicate that bacteria or their products probably play a role in the cause of death^{47, 48}. Here again the protection afforded is limited, and the existence of some other lethal agent is further indicated by the series herein reported.

The lethal action of the contents of a strangulated loop of gut has been shown by many workers,^{40, 42, 43, 50, 66, 67} but heretofore there has been no conclusive evidence for the absorption into the blood stream of the intraluminal contents, nor can it be stated that death would result even if such substances were absorbed.

The occlusion of the veins to a segment of bowel as occurs in experimentally produced strangulation precludes this route as a source of absorption. Lymphatic absorption has been incriminated by some investigators,^{40, 43, 49} but others have failed to prolong life by obstructing the lymphatics^{67, 68}. The likeliest source of absorption would appear to be from the peritoneal cavity^{44, 45, 68}. However, in practically all instances reported, the peritoneal fluid removed from strangulated animals has proved to be nontoxic when injected into other animals,^{42, 46, 50, 57, 69} thus indicating that noxious agents from the lumen had not entered the peritoneal fluid or else that the noxious agents were not present in sufficient amount to be lethal when injected into other animals.⁶⁷

Our studies have revealed that late in the course of strangulation obstruction in animals intensively treated to avoid hemorrhage, shock, dehydration, and electrolyte imbalance, the bowel wall becomes permeable to its intraluminal contents, and this fluid then passes out into the peritoneal cavity and thence into the blood stream. We believe, as do others,^{39, 40, 45, 49, 56, 64} that the pink peritoneal fluid is but a filtrate of the circulating blood. We also think that the development of the reddish-black or black fluid is due to a filtration of

the strangulated gut contents through the devitalized bowel wall into the peritoneal cavity. Even after the complete occlusion of the venous channels, evidence of permeability of the gut wall to its intraluminal fluid occurred in none of our animals before 28 hours. This is longer than the length of survival of animals in which shock, dehydration and electrolyte balance have not been combatted.

That this black fluid is a "diluted" counterpart of the gut contents is also shown and would be expected in view of the continued outpouring of the pink or plasmalike fluid from the peritoneal surfaces in the presence of a devitalized segment of intestine within the peritoneal cavity⁵⁷.

The death of the animal followed shortly after the development of the reddish-black or black fluid in the peritoneal cavity. In view of this fact and the known marked toxicity of the lumen contents, it would appear that some lethal factor was present in this later fluid. It is unlikely that the living bacteria or their end products are directly concerned with the death of the animal^{43, 57}. While it is true that the black fluid contained, qualitatively, the same organisms as did the lumen contents just before death, it must also be remembered that these same organisms were present in the pink fluid from around 16 to 20 hours onward, yet death did not occur until a short time after the development of the black peritoneal fluid. The important role of the organisms indirectly by their action on the devitalized mucosa, however, has been indicated by Sarnoff and Fine²² and Blain, *et al*,^{47, 48} and it is likely that the prolongation of life in the penicillin treated group of animals reported by Blain *et al*^{47, 48} was due to the fact that the destructive action of the organisms on the bowel wall was delayed, thereby lengthening the time in which the gut became permeable to its intraluminal contents.

If it is true that a noxious agent formed in the gut and absorbed into the blood stream is the cause of death in these animals, then much clarification of the route of absorption is afforded by our studies. Although the characteristic luminal contents were present within the lumen as early as 12 hours, death did not occur until soon after the reddish-black or black fluid had appeared in the peritoneal cavity, and in no case were we able to demonstrate spectrophotometrically the hemin or hemoglobin derivative in the blood stream until after it had appeared in the peritoneal cavity. The absorption from the lymphatics of the strangulated gut would, therefore, appear to be negligible.

While the characteristic absorption spectrum curve typifying black bowel contents and black peritoneal fluid has been defined, the identity of the pigment or pigments responsible for the abnormal spectrum has not been established. It remains for future investigation to establish whether the curve represents hemoglobin derivatives not hitherto described and originating from the blood pigment under the abnormal conditions in the strangulated bowel segment, or whether the spectrum is that of a mixture of common hemoglobin derivatives with less usual ones. Among the latter may be mentioned sulfhemoglobin⁵⁹ and porphyrins,⁷⁰ both of which types of pigments could conceivably

be formed in the intestine from hemoglobin. At present we have no evidence that either of such pigments is involved.

It is important to state clearly that at this stage we have no evidence whatever directly implicating the abnormal pigment or pigments with responsibility for the toxicity. Such close hemoglobin derivatives as methemoglobin are essentially nontoxic,⁷¹ and at present there is little evidence that other derivatives or relatives of hemoglobin may be toxic, with the possible exception of porphyrins. It is sufficient to state that the pigments responsible for the abnormal spectrum are contained in the black peritoneal fluid, characterize it, and give evidence for its intestinal origin.

SUMMARY AND CONCLUSIONS

1 Late in the course of strangulation obstruction the bowel wall becomes permeable to its intraluminal contents, and this characteristically colored fluid passes out into the peritoneal cavity and is then absorbed into the blood stream. The death of the animal occurs soon after the appearance of this late black or reddish-black fluid in the peritoneal cavity.

2 By spectrophotometric analysis we have demonstrated that the character of the intraluminal contents is due in part to the presence of a hemin or hemoglobin derivative hitherto unreported *in vivo*, and by this method we have directly followed its passage from the gut lumen into the peritoneal cavity and from thence into the blood stream.

3 In view of the close correlation between the appearance of the black peritoneal fluid and the demise of the animal, it would appear likely that a lethal agent was present in this late fluid. If this is the true explanation, the "toxicity" of this fluid should be demonstrable on injection into recipient animals, and the subsequent report is concerned with this phase of the problem.

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THE CAUSE OF DEATH IN STRANGULATION OBSTRUCTION AN EXPERIMENTAL STUDY

II LETHAL ACTION OF THE PERITONEAL FLUID*

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IN OUR FIRST COMMUNICATION¹ we showed that, late in the course of strangulation obstruction in dogs intensively treated for shock, dehydration, and electrolyte imbalance, the peritoneal fluid changed from a pink, odorless, coagulable fluid to a reddish-black or black, malodorous, non-coagulable fluid. In view of the rapid demise of the animal after the appearance of the black fluid in the peritoneal cavity and its rapid absorption into the blood stream, it seemed likely that some lethal factor was present in this fluid. This report is concerned with the injection of the peritoneal fluid, removed from the strangulated animals at various intervals, into normal animals by both intravenous and intraperitoneal routes.

METHOD

Normal, unanesthetized dogs were used as recipient animals. In no case was the circulating blood volume decreased² before injection. The total amounts of fluid were in all cases delivered intraperitoneally between two and eight hours. Intravenous injections were given either by rapid drip into a leg vein if the amount was large, or slowly by syringe injection if the amount was small. Following injection, the animals were carefully observed, and the temperatures were followed in a number of the dogs. Peritoneal fluids were kept in the ice box at all times between sample collection and administration and warmed to room temperature just before administration. The fluid was, in all cases, injected unchanged within a few hours after collection. In those animals which appeared to be moribund, blood was taken for culture and for spectrophotometric analysis. All animals, except No. 11, were posted immediately after death.

RESULTS AND DISCUSSION

The injection of peritoneal fluid or gut contents from animals having a strangulation obstruction into normal animals has been used by many investigators as a method of determining the toxicity of these substances. While

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the criteria for "toxicity" have varied,^{3,5} the peritoneal fluid almost uniformly, has been shown to have essentially no effect on the recipient,^{2, 6, 12} even when injected in amounts up to 200 cc,⁴ and the late gut contents have been shown almost invariably to cause death in such small amounts as several cc's.^{8, 9, 13, 14} It is of interest to note, however, that Foster and Hausler¹⁰ injected 80 to 100 cc of loop fluid, filtered through sterile gauze only, from strangulated dogs dying between 7 and 12 hours, intraperitoneally into recipient animals without causing death.

In this study the criterion for toxicity of the peritoneal fluid was the death of the animal. Although occasional vomiting and diarrhea followed the injection of very large amounts of pink fluid, if death did not ensue the injection was recorded as having "no effect." Obviously, the amount of fluid to be injected was, as in the past, purely arbitrary. However, we feel that much clarification of this point may be gained by (1) a comparison of the total amounts of pink fluid and red-black or black fluid injected, and (2) our spectrophotometric studies.

A review of Table I reveals the following. The pink, odorless, coagulable peritoneal fluid which was present up until several hours before death in the strangulated animals did not cause the death of the recipient in any of six animals injected either intraperitoneally or intravenously in amounts up to 40 to 50 cc per Kg of body weight. We have injected intravenously as much as 425 cc of this fluid into an animal over a period of one hour without any effects except a mild transient vomiting. In many cases this pink peritoneal fluid was withdrawn as late as 24 to 28 hours after strangulation.

It is of interest that the bacterial flora of this pink fluid was practically identical with the reddish-black, or black, fluid qualitatively and death was not caused by injection of the bacteria.^{8, 11}

The animals which received the reddish-black or black fluid behaved in a different manner. Four of the seven animals so injected died, two at six and seven hours after intraperitoneal injection, and the remaining two at five hours and 30 to 40 hours after intravenous injection. Another animal (No. 13) died five days after receiving red-black fluid intravenously. It was thought that the death of this animal was due, at least in part, to distemper, and it is therefore not considered as one of the animals dying from the injection. It is true that large amounts (35 cc per kilo) of the black fluid were given intraperitoneally, but even these amounts were considerably less than the pink fluid given either intraperitoneally or intravenously. Of the two dogs that died following intravenous administration, it will be noted that one died five hours after receiving only 24 cc, and the other died between 30 to 40 hours after receiving 100 cc.

The reactions of the animals which died were similar in all cases whether the fluid was given intravenously or intraperitoneally. Up until around two hours after injection the animals appeared normal. After this period, however, their condition rapidly deteriorated, vomiting became more frequent and severe, and the animals were usually moribund several hours before death.

TABLE I—*Lethal Action of the Peritoneal Fluid*

Peritoneal Fluid Injected											
Recipient Animal	Weight (kg)	Source	Hrs Between Strangulation and Withdrawal	Character of Fluid	Organisms Present	Amount— Total Cc	Amount— Cc /Kg	Method	Interval of hrs Given	Comment	
1	9 0	331	3½-24	Pink odorless coagulable	Hemo clostridia	400	45	I P	8	No effect	
2	2 0	232	12-28	Pink odorless coagulable	Hemo clostridia B coli Salmonella	350	50	I P	4	No effect	
3	7 0	357	24 or less	Pink odorless coagulable	B Coli Hemo strep	280	40	I P	2	No effect	
4	7 0	347	24 or less	Pink odorless coagulable	Hemo clostridia B coli Non hemo strep Non hemo clost A aerogenes	210	30	I V	2½	No effect	
5	6 7	295	24 or less	Pink odorless coagulable	B coli Hemo strep Non hemo strep	300	45	I V	3	No effect	
6	8 5	365	20-25	Pink odorless coagulable	Hemo clostridia B coli Hemo strep Non hemo strep A aerogenes	425	50	I V	1	No effect	
7	9 0	331	28-32 36 42	Pink odorless coag Reddish black Black foul non coag	Hemo clostridia 100 B coli 100 Strep vividans 160	360	40	I P	3	No effect	
8	10 0	235	28-32	Black foul non coagulable	Hemo clostridia B coli Hemo strep Non hemo strep Non hemo clost Hemo clostridia B coli Hemo Strep Non hemo strep Non hemo clost A aerogenes B proteus	350	35	I P	1¼	Died 6 hrs	
9	10 0	357	35	Black foul non-coagulable	Hemo clostridia B coli Hemo Strep Non hemo strep Non hemo clost A aerogenes B proteus	350	35	I P	6	Died 7 hrs	
10	7 3	357	35	Black foul non coagulable	Hemo clostridia Hemo strep Non hemo strep Non hemo clost A aerogenes B proteus	24	3	I V	At once	Died 5 hrs T =107 ¹	
11	5 5	347	29 30	Red black non coag Black foul non coag	Hemo clostridia Hemo strep Non hemo strep 35 Non hemo clost 65 A Aerogenes B proteus	100	18	I V	2	Died 30-40 hrs T =104 ⁸ at 4½ hrs	
12	8 0	365	28¼	Red-black faint odor non coag	Hemo clostridia B coli	155	19	I V	2	No effect	
13	8 3	365	28	Red black faint odor non coag	Hemo strep A aerogenes	125	15	I V	1	Died 5 days —distem- per T =105 ² at 4½ hrs	

The animal which lived for 30 to 40 hours was listless and obviously sick during this entire period. No temperatures were taken in the animals receiving the intraperitoneal injections, but it will be noted that the temperature was 107°F just before death in one of the animals receiving an intravenous injection, and 104°F at approximately the same time after injection in the other. This is interesting in view of the high temperature elevation observed terminally in the strangulated animals.¹ Blood cultures drawn 45 to 65 hours after the injection into the recipient animals which died were negative on direct inoculation onto blood agar in three cases, and positive for *B. Coli* in the remaining case.

The necropsy findings in the two animals which died following intra-peritoneal injection were identical and limited to the abdomen. The peritoneum was mildly injected in areas. The peritoneal cavities contained 150 cc (No. 8) and 275 cc (No. 9) respectively, of a red-brown fluid somewhat similar to that injected. In both cases there was an intense injection of the mesentery especially marked as the mesentery approached the bowel. The duodenal mucosa, and the jejunal and ileal mucosa to less extent, showed submucosal hemorrhages. Aside from a moderate congestion of all the abdominal viscera, no other pathologic findings were noted. No gross abnormalities were noted at necropsy in the animals receiving the intravenous injection.

While our overall results with injections of the peritoneal fluid clearly indicated the great toxicity of the black peritoneal fluid, nonetheless, there appeared to be marked variations in the toxicity of this fluid from different animals. Variations in the character of the black or red-black fluid, as suggested clinically by the different responses, was objectively confirmed by our spectrophotometric studies, and the cause for this variation was conceivably explained by a review of the intake and output data for the strangulated animals. The peritoneal fluid from dog No. 357 was lethal when only 24 cc was injected intravenously. This peritoneal fluid gave a spectrophotometric curve (Curve 3, Fig. 1) very similar to the one given by the bowel contents from this animal, and would be expected since approximately 500 cc of intraluminal contents passed into the peritoneal cavity in the last few hours of survival. The fluid from dog No. 347 was lethal to the recipient at 30 to 40 hours after 100 cc intravenously and the change toward the characteristic abnormal spectrum was less marked. As we were completely aspirating the strangulated lumen in this animal, less fluid passed out into the peritoneal cavity, and therefore, the dilution factor by the pink fluid was greater. Direct evidence of this was obtained from the values for original concentration of total pigments as cyan-methemoglobin. The peritoneal fluid of dog No. 365 (no death in recipients with 155 and 125 cc respectively intravenously) showed the least marked spectrophotometric changes (Curve 4, Fig. 1), and here again, the dilution factor was of considerable magnitude.

The degree of toxicity as expected was greater in those animals in which a greater amount of the lumen contents diffused through the wall into the peritoneal cavity. This is borne out by the fact that the gut lumen was almost

devoid of fluid at post mortem in two animals having highly toxic fluids (No 235 and 357, Curves 2, 3, Fig 1), whereas almost 600 cc of peritoneal fluid in each was present despite the fact that the peritoneal cavity was evacuated as completely as possible less than four hours before death. Animal No 347 developed almost 300 cc of black peritoneal fluid despite the fact that 200 cc of gut contents was removed one hour prior to death, and the peritoneal fluid from this animal was also lethal.

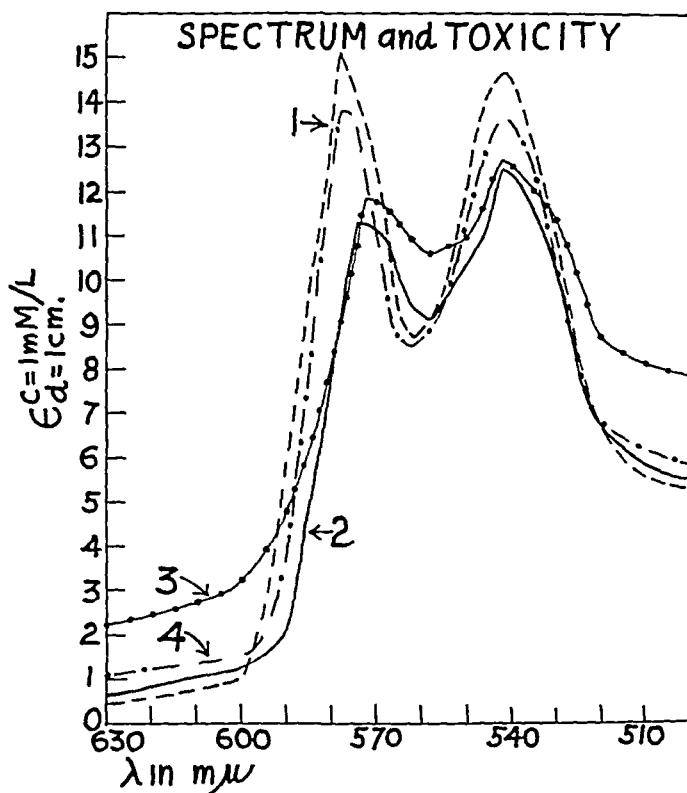


FIG 1—Data illustrating the relationship of toxicity to degree of spectral abnormality in comparison with normal oxyhemoglobin spectrum

Curve 1 Absorption spectrum curve of unchanged oxyhemoglobin

Curve 2 Absorption spectrum curve of peritoneal fluid (highly toxic) collected at 32 hours after strangulation from dog No 235. Original concentration of total pigment as cyan-methemoglobin was 4.46 Gm per 100 ml

Curve 3 Absorption spectrum curve of peritoneal fluid (highly toxic) collected at 35 hours from dog No 357. Original concentration of total pigment as cyan-methemoglobin was 1.14 Gm per 100 ml

Curve 4 Absorption spectrum curve of peritoneal fluid (relatively nontoxic), collected at 28 hours from dog No 365. Original concentration of total pigment as cyan-methemoglobin was 3.24 Gm per 100 ml

We have stated¹ that the demonstration of an abnormal pigment, present first in the strangulated lumen, later in the peritoneal fluid, and finally in the blood, has been a useful method of following the course of events in the

strangulated animals From the results herein reported, this finding assumes greater significance It would appear that some relationship exists between the content of unidentified pigments responsible for the abnormal spectrum of the black peritoneal fluid and its toxicity Some relationship is also indicated by the fact that one of the six animals which died following strangulation had only 40 cc of black fluid in the peritoneal cavity at death and this fluid showed the most marked changes spectrophotometrically of any obtained Also, it will be remembered that the altered curves were not obtained in the gut contents until around 12 hours In view of the fact that Foster and Hausler¹⁰ injected large amounts of less than 12 hour loop fluid into other animals intraperitoneally without causing death, a relation between the altered pigment and the toxicity of the fluid seems indicated

CONCLUSIONS

1 The pink or strawberry colored peritoneal fluid, removed from animals with a strangulation obstruction, which owes its character to the presence of blood and unchanged hemoglobin, is non-toxic on injection into normal, recipient animals either by the intraperitoneal or intravenous routes even when rapidly administered in amounts up to 50 cc per Kg of body weight

2 The late or black peritoneal fluid, which has been shown to be derived at least in part from the lumen of the strangulated gut is lethal on injection into normal, recipient animals by either the intraperitoneal or intravenous routes when administered in much smaller amounts than the pink fluid

3 The toxicity of the peritoneal fluid samples removed in experimental strangulation obstruction bears a relationship of proportionality to its content of unidentified pigments responsible for the abnormal spectrum of the black peritoneal fluid

4 It must be stressed that while the abnormal spectrum characterizes the toxic fluid, and, indeed, has served as a measure of the degree of toxicity of the fluid on injection into other animals, no evidence is at present at hand to identify the pigment itself as the toxic agent

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FIBROUS DYSPLASIA OF BONE*

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OUR INTEREST in fibrous dysplasia of bone was aroused in 1947 by observation of a patient (Case 6) with lesions of the ribs which were thought, on roentgenologic examination, to be cysts. However, exploration of a rib revealed solid tissue, and microscopic examination showed a picture unlike that usually seen in osteitis fibrosa cystica. Comparison of our findings with those described by Albright and his associates^{2, 3} and Lichtenstein and Jaffe³² led us to believe that this patient had the disease which the latter authors called fibrous dysplasia of bone. Subsequently another patient was seen who showed similar roentgenologic, operative and microscopic findings. We reviewed the records, roentgenograms and microscopic sections of all patients seen at the Vanderbilt University Hospital since 1925 who had been diagnosed as having had giant-cell tumor, solitary bone cyst, osteitis fibrosa cystica or Paget's Disease (osteitis deformans). We discovered no cases of fibrous dysplasia previously diagnosed as giant-cell tumor or Paget's Disease but found four instances formerly thought to be osteitis fibrosa cystica and one case originally thought to be a solitary bone cyst. Inasmuch as the status of this syndrome as an entity is still the subject of clinical investigation and few follow-up studies have been recorded, it was thought justifiable to report our observations in seven such patients.

HISTORICAL REVIEW

The first case of what is thought to be the disease under discussion was reported in Europe in 1922 by Wieland³⁸. In England, Telford⁷³ in 1931 reported one "case of osteitis fibrosa with formation of hyaline cartilage" which was probably an example of fibrous dysplasia of bone. Hunter and Turnbull²⁴ in 1931 reported four cases under the title of focal osteitis fibrosa. In 1932 Braid⁶ described such a case and attempted to separate this syndrome from osteitis fibrosa cystica. In this country attention was directed to this syndrome in 1937 when Albright and his associates² described five cases of a "syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females". In 1938, Lichtenstein³¹ reported similar findings in eight patients and employed the term "fibrous dysplasia of bone".

Some of the many terms which have been applied to this disease are Albright's syndrome,^{4, 12, 13, 20} polyostotic fibrous dysplasia,^{10, 11, 14, 17, 30, 31, 35, 37} osteodystrophia fibrosa,^{16, 38, 52} localized von Recklinghausen's disease,⁵⁴

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osteitis fibrosa disseminata,^{9, 45, 46, 51} regional fibrocystic disease,¹ fibrocystic disease of bone,^{22, 42} osteodystrophia disseminata⁵⁵ and focal osteitis fibrosa^{24, 53} We have used the term "fibrous dysplasia of bone" because it is the one used by the majority of workers who have recently written about this subject In view of the many terms applied to this disease it is impossible to discover all such cases which have been reported but the appended bibliography is as nearly complete as possible

INCIDENCE

Age The ages of our patients (Table V) on admission ranged from 5 to 61 years Inasmuch as some observers^{15, 17, 25, 26, 28, 30, 32, 34} have stated that



FIG 1—Case 1 (A) There is sclerosis of the bones of the base of the skull, the inferior portion of the frontal bone and the temporal bone The areas which appear to be rarefied are normal convolutional markings

(B) There are areas of rarefaction and spontaneous fracture in each femoral neck with evidence of healing on the right Other bones involved in this patient are listed in Table I

this disease usually begins in childhood, it is noteworthy that in one of our patients (Case 2) the age on admission was 61 years and the symptoms were of only two days duration However, it is obvious that the exact age of onset of his disease could not be determined

Sex There were five males and two females

Race There were four white and three Negro patients although the ratio of white to Negro patients admitted to the Vanderbilt University Hospital is nine to one In Schlumberger's⁴⁴ report of 67 cases of fibrous dysplasia of bone, only two of the patients were Negroes

Site Tables I and II show the sites of involvement of bone

CLINICAL MANIFESTATIONS

Duration (Table V) The shortest duration of symptoms before admission was two days (Case 2) and the longest was 16 years (Case 6) The other

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five patients had had symptoms relating to the disease being reported for one week, three weeks, three and one-half months, seven and eight years

Symptoms related to bone There were spontaneous fractures in four patients and the remaining three individuals had pain, although fracture had

TABLE I

Case	Surg Path No	Bones Involved
1	6313	Skull, femora, tibiae fibulae, radii humeri ulnae 4 metacarpals and 3 phalanges
2	6601	Upper shaft left femur
3	8380	Right 10th rib
4	10164	Intertrochanteric region right femur
5	16285	Left tibia (multiple areas)
6	21577	Left 5th 6th 8th and 12th ribs Right 12th ribs
7	21914	Right 9th 10th and 12th ribs

not occurred There was disability in all instances, even in the patients with involvement of only the ribs In the patient with involvement of a bone of the lower extremity in whom there was no fracture, a limp had been present for two days before admission A tumor had not been noted in any instance

Age of onset of puberty Lichtenstein and Jaffe³² collected 90 cases of fibrous dysplasia, of whom 51 were females, 35 were males, and in four the

TABLE II

	Bones Involved				
	Number of Cases	Number of Bones	Epiphysis	Diaphysis	Metaphyseal Region of Diaphysis
Ribs	3	9	0		
Femur	3	4	0	6	3
Tibia	2	3	0	3	0
Fibula	1	2	0	2	1
Humerus	1	2	0	2	0
Skull	1	1	0		
Ulna	1	2	0	2	0
Radius	1	2	0	3	2
Metacarpals	1	4	0	4	0
Phalanges	1	3	0	3	0
Total	15*	32	0	25	6

* The apparent discrepancy in the total (15) when there were actually only seven patients is due to the fact that more than one bone was involved in three patients

sex was not recorded Precocious puberty was noted in 20 of the former and in none of the latter In our two female patients, the menarche occurred at the age of 12 years in Case 5, a Negress, and at 11 years in Case 6, a white woman

Renal symptoms None of our patients had symptoms suggestive of renal calculus

Family history There was no family history of bone disorder or of neurofibromatosis, but the paternal grandfather of one patient (Case 1) had "brownish splotches" on his back

Examination of the bones There was no palpable tumor at the site of involvement of any bone in which there was no fracture. However, tenderness over the diseased areas was present in all seven patients, in four of whom fractures were present. Several authors^{2, 3, 12, 15, 17, 18, 25, 37, 43} have observed premature skeletal growth and maturation in girls with the florid form of fibrous dysplasia. Such findings were not present in any of our patients, only two of whom were females and but one of the two (Case 6) having had the disease in the "florid form."

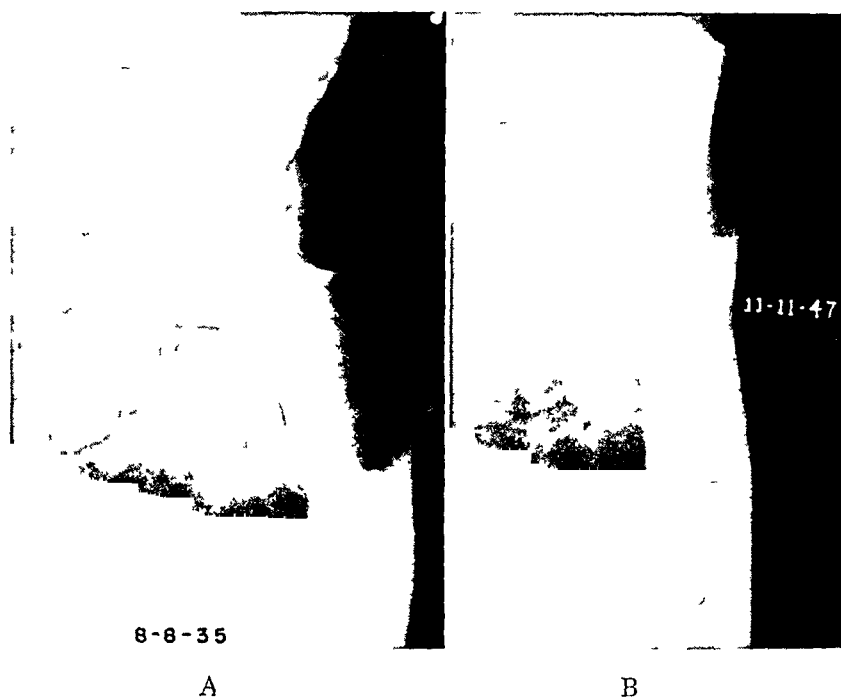


FIG 2—Case 2 (A) There is a lesion of the shaft of the left femur just distal to the lesser trochanter. The cortex is slightly expanded, the margins are quite dense and the lesion is sharply circumscribed. No spiculization is seen. This lesion resembles a latent bone cyst and, although exploration revealed solid tissue, originally the contents may have been cystic.

(B) This film of the left femur made 13 years following curettage and phenol cauterization shows that the area has been almost completely filled in with dense bone.

Skin Three patients had areas of pigmentation of the skin (Table V). In Case 7, a Negro male, there was an abnormality which we believe has not been described previously in connection with this disease and which may or may not be significant. Just inferior to the left nipple there was markedly decreased pigmentation of the skin (Fig 6A) over an area 3 by 6 cm. in size. This spot was not elevated and did not differ in texture from the surrounding skin but its appearance was quite striking in contrast to the fairly dark brown skin elsewhere on the body. This patient had fibrous dysplasia of the right ninth, tenth and twelfth ribs.

Thyroid In 90 cases collected and reported by Lichtenstein and Jaffe¹² hyperthyroidism was present in four patients, one of whom was a male and three of whom were females. Although none of our patients showed evidence of hyperthyroidism, one woman (Case 6) had a basal metabolic rate of minus 23 per cent. She had had six spontaneous abortions with no evident cause other than the hypothyroidism.

ROENTGENOLOGIC FINDINGS

As seen on the roentgenogram, the bone lesions were usually irregular areas of rarefaction which varied greatly in size and shape. In Case 5 (Fig 4A) there were several small areas measuring only 3 or 4 mm in diameter,



FIG 3—Case 4 (A) There is a solitary lesion of the neck and upper part of the shaft of the right femur. Spiculation, sharp demarcation and a fracture may be seen. The cortex is expanded.

(B) This roentgenogram, made more than ten years after the one shown in Fig 3A, shows that most of the area, previously exhibiting decreased density, has been filled in with normal bone. There are four small areas of decreased density.

whereas in Case 3 the pathologic process involved almost the entire length of the tenth rib. The "ground glass" appearance of the rarefied areas usually led the roentgenologists to believe that the lesions were cystic. Bony trabeculae were seen projecting into the areas of increased penetration in all instances except Case 2 (Fig 2A). In Fig 6D these trabeculae are clearly shown in the roentgenogram of an excised rib. Except in one instance, there was expansion of the bone with thinning of the cortex in all lesions over 5 mm in diameter. Case 6 (Fig 5A) showed disruption of the cortex of a rib. In three patients (Cases 2, 4, and 5) bone of increased density was seen around the margins of the areas of decreased density.

In each of three patients the lesion was single (Figs 2A and 3A), in one patient there were multiple lesions in a single bone (Fig 4A) and in three individuals there was involvement of multiple bones (Figs 1A, 1B, 5A, 5B, 6B and Tables I, II and V).

The portions of the skeleton not involved by fibrous dysplasia showed normal bone structure. In the four patients in whom there were multiple lesions of one or more bones, the bone between the areas of rarefaction appeared normal on the roentgenogram. There was no instance of generalized bone decalcification such as is seen in hyperparathyroidism.

TABLE III

Laboratory Findings

Case No	Blood Calcium Mgm %	Blood Phosphorus Mgm %	Alkaline Phosphatase Bodansky Units	B M R (%)	Calcium Metabolism
1	10.6	2.5	Not done	Not done	Normal
2	11.8	3.12	4.7	4	Not done
3	11.4	3.75	Not done	Not done	Not done
4	11.1	4.6	Not done	Not done	Not done
5	12.7	4.8	5.6	Not done	Not done
6	10.6	3.3	2.7	-21 -23	Normal
7	11.2	3.0	4.4	Not done	Not done

Fractures were seen in four patients, one individual having had fractures of three bones.

In the single patient in whom the skull was involved (Fig 1A) the bones near its base showed dense sclerosis and thickening. Such findings correspond with those of Furst and Shapiro,¹⁷ Pugh⁴¹ and Windholz.^{59, 60}

A tentative diagnosis of fibrous dysplasia of bone should be made if the bone involvement is multiple and predominantly unilateral.

TABLE IV

Operative Findings

Case	Cortex	Color	Consistency	Cysts
1	Not recorded	Not recorded	Cartilaginous	None
2	Dense	Yellow and grey	Firm friable	None
3	Thin	Whitish	Firm	None
4	Not recorded	Reddish	Soft friable	None
5	Thin	Yellow	Friable gritty	None
6	Thin (1 mm)	Fibrous tissue	Firm, gritty	None
7	Thin	Reddish brown	Firm rubbery gritty	One

LABORATORY FINDINGS

The laboratory studies are shown in Table III. The phosphorus levels were normal and the calcium levels were at the upper limits of normal or slightly elevated.

OPERATIVE FINDINGS AND GROSS PATHOLOGIC CHANGES

After reviewing the clinical manifestations and roentgenograms of his patient, a surgeon who has not previously seen this syndrome usually expects to find at operation a cavity containing fluid. However, in all seven of our patients, exploration of the bone revealed solid tissue and in only one of them

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was there any tissue which was not solid. In Case 7, there was a 1.5 by 1 cm cyst containing yellow fluid but the remainder of the rib showed solid fibrous tissue.

The cortex of the bone was thinned in four of the five instances in which its thickness was described (Table IV). The color of the pathologic tissue varied from white through yellow to reddish-brown, depending upon the amount of hemorrhage which was present. The consistency in one instance was soft and friable but in the others it was firm. The "gritty feeling" due to



FIG 4—Case 5 (A) In the distal portion of the shaft of the tibia there is a large expansile lesion with spiculation and sharply defined, slightly sclerotic margins. In the inferior portion of the rarefied area there is a fracture line which extends distally into the otherwise normal bone. Above the large lesion, several small, round, punched-out areas of decreased density are present. (B) Six and one-half months after curettage of the large lesion, the roentgenogram shows that the area of rarefaction has become filled in with dense bone and that the fracture has healed.

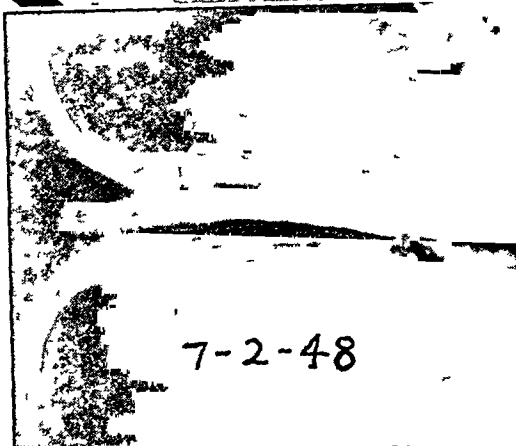
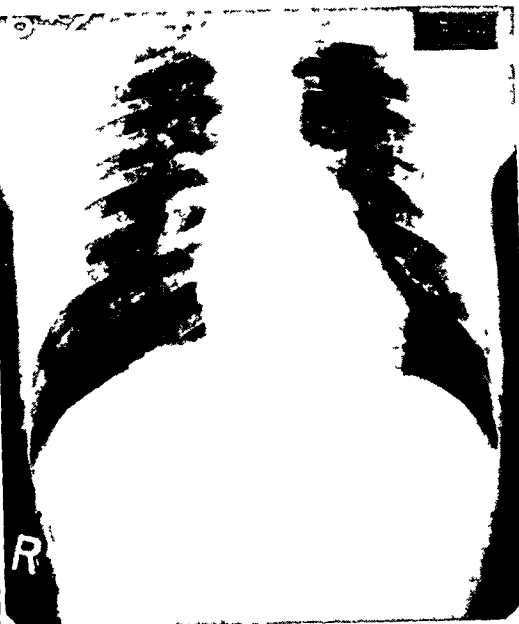
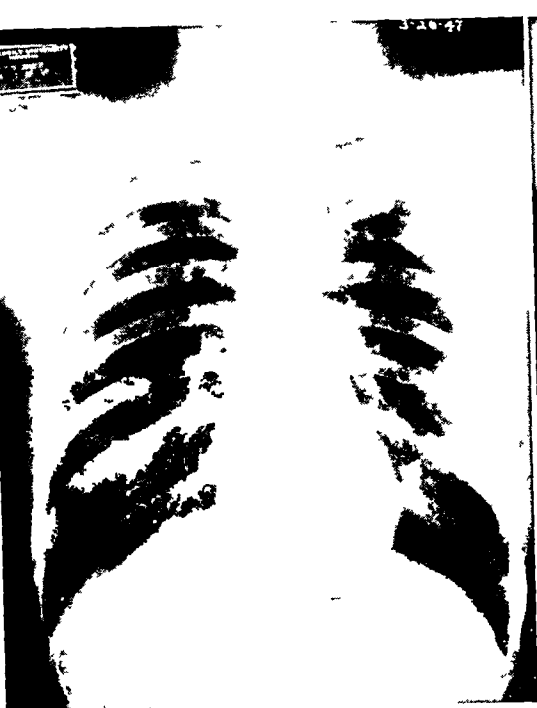
the presence of spicules of bone was recorded in only three instances but the microscopic sections led us to believe that these spicules must have been present in all of the patients.

MICROSCOPIC PATHOLOGIC CHANGES

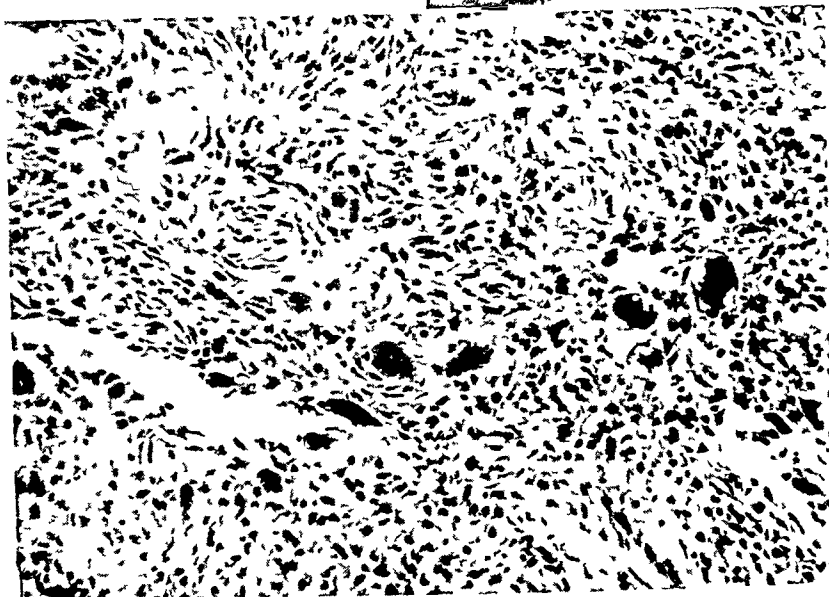
Upon microscopic examination alone, one can positively differentiate fibrous dysplasia from giant-cell tumor, but not from solitary bone cyst or osteitis fibrosa cystica. The two constant findings are connective tissue and osteoid tissue (Fig 6E). The term "osteoid tissue" is somewhat equivocal, by it we imply that the tissue is young bone which has not been calcified. The areas of new bone formation ranged from acidophilic osteoid tissue to adult calcified bone. In only one instance (Case 6, Fig 5E) were giant cells seen.

A

B



D



E

FIG 5—Legends on opposite page

and these cells were readily distinguishable from those seen in giant cell tumor by the fact that their nuclei ranged from two to ten in number instead of from 15 to 200. In the cytoplasm of most of these multi-nucleated cells there were vacuoles varying in number from one to seven. When viewed under polarized light, these vacuoles were seen not to be doubly refractile. In one instance (Case 7, Fig 6E) the fibrous process was seen extending into the surrounding muscle in the absence of a fracture demonstrable on the roentgenogram. In this patient, the cortex elsewhere was only one millimeter in thickness. Irregular fragments of old bone were seen in several instances. Cartilage other than that which is normally present was not seen.

FOLLOW-UP STUDIES

The follow-up data are presented below and in Table V and Figures 2B, 3B, 4B and 5B.

Case 2 On March 22, 1935, osteotomy of the femur with curettage and cauterization with carbolic acid was done. One month later, the roentgenogram showed some regeneration of bone in the operative area. Three months after operation the roentgenogram showed that there had been some regeneration of bone. Ten months after operation, there was seen on the roentgen ray film almost complete healing of the operative area. On November 11, 1947, more than 12 years after operation, the patient stated that he had had no symptoms referable to the lower extremity or hip. The roentgenogram showed that the previously diseased area had filled in with dense bone (Fig 2B).

Case 3 On November 18, 1936, the tenth rib was removed. On December 1, 1947, 11 years after operation, the patient stated that he had had no pain in the ribs or any other bones and on that date the roentgenograms of the chest showed no evidence of disease in the remaining ribs.

Case 4 On July 11, 1938, the diseased area in the femur was curetted and bone chips were placed in the cavity. Four months later the roentgenogram showed that the rarefied area, except for about 2 cm, had filled in with normal bone. Nine months after operation, the roentgenogram showed almost complete restoration of normal bony density throughout the femur. On August 28, 1948, (Fig 3B) more than ten years after operation, there were no symptoms and the roentgenogram showed that most of the formerly diseased area had filled in with normal bone but that there were four small areas of decreased density present.

Case 5 On February 25, 1943, osteotomy with curettage of the tibia was done. Three months later the roentgenogram showed that the fracture had healed. Six months after operation, there was normal function of the extremity and the roentgenogram (Fig 4B) showed that the large area which previously had shown decreased density was filled in.

FIG 5—Case 6 (A) This chest film shows lesions of the left fifth, sixth and eighth ribs. Both twelfth ribs were involved also. There has been little change in these lesions since a roentgenogram (not shown) was made elsewhere three years previously.

(B) The roentgenogram of the chest shows that there has been no change in the lesions of the ribs over a period of fifteen months.

(C) Photograph of the excised eighth rib which is shown in Fig 5A.

(D) Roentgenogram of the gross specimen shown in Fig 5C.

(E) Multi-nucleated giant cells are shown. There are eight nuclei in the cell just to the left of and below the center of the figure. There are fewer nuclei in the other giant cells.

with dense bone but the small areas of decreased density were still visible. This patient was not seen by us subsequently but in 1947, four years after operation, it was reported by mail that she had had no further symptoms referable to the tibia or any other bone.

Case 6 On March 31, 1947, an osteotomy of the left eighth rib was done and tissue was removed for microscopic study. This patient continued to have pain in the chest, most severe in the region of distribution of the eighth intercostal nerve. On June 25, 1948, the roentgenogram (Fig 5B) showed that there had been no change since the examination 15 months previously (Fig 5A). On July 2, 1948, the eighth rib along with the eighth intercostal nerve was excised (Figs 5C and 5D). The pain decreased immediately after operation and on August 19, 1948, she stated that her pain had been completely relieved.

Case 7 On June 5, 1947, the tenth rib was excised. On June 18, 1948, one year later, the patient stated that he had had no pain. The roentgenogram showed that the



FIG 6—Case 7 (A) Photograph of the area of decreased pigmentation (B) There is a large lesion in the right tenth rib which shows expansion of the cortex and extensive spiculation. There is a smaller lesion in the vertebral end of the tenth rib, separated from the more lateral lesion by normal bone. The neck of the ninth and that of the twelfth ribs show rarefaction and trabeculation.

tenth rib had been excised except for the head, in which the diseased area was unchanged, and that there had been no change in the lesions in the ninth and twelfth ribs.

COMMENT

The clinical and roentgenologic manifestations of fibrous dysplasia in a single site and those of solitary bone cyst are almost identical and microscopic examination of the material from lesions of fibrous dysplasia reveals findings quite similar to those seen in the lining of a bone cyst. In both diseases, healing often occurs following spontaneous fracture or curettage. Hence, it is not extremely important to distinguish between these lesions. However, it is necessary to differentiate fibrous dysplasia in its polyostotic form from osteitis fibrosa cystica to prevent the patient's being subjected to a search for a parathyroid adenoma. In three of the seven cases being reported, neck

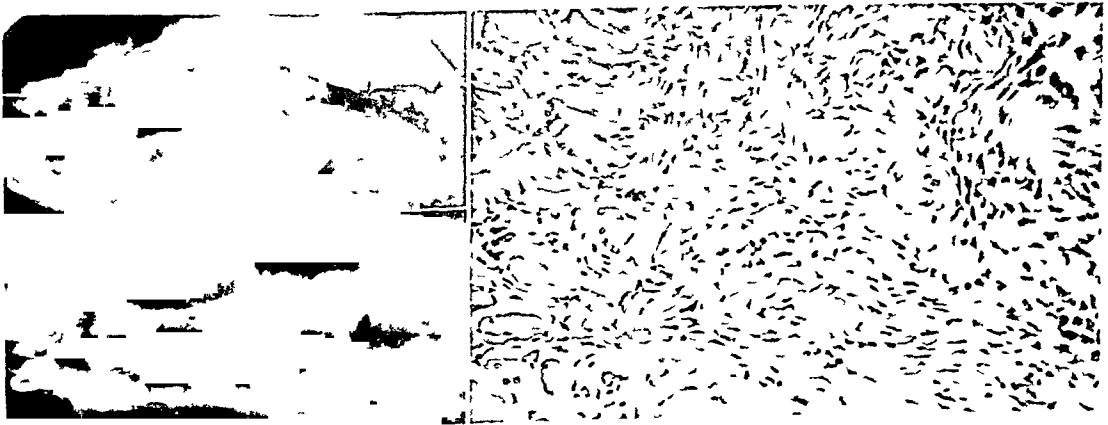
exploration was done, one of which resulted in death upon the operating table. No parathyroid tumor was found in any of the three patients. The laboratory findings of normal phosphorus levels and calcium levels which are normal or only slightly elevated, plus the operative finding of solid tissue in the bone

13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32



C

FIG 6—(C) Photograph of the excised tenth rib



D

E

FIG 6—(D) The roentgenogram of the excised tenth rib shows translucent areas traversed by bony trabeculae. The translucent areas on the roentgenogram, indistinguishable from cysts, were composed of fibrous tissue except for one cyst which was 1.5 by 1 cm. in size.

(E) On the left there is striated muscle which has been invaded by the fibrous process. The central portion shows connective tissue and the right side shows osteoid tissue.

instead of fluid, are nearly always adequate criteria upon which to make this differentiation. With equivocal findings it may be necessary to demonstrate the absence of negative calcium balance in order positively to rule out the presence of hyperparathyroidism.

Our follow-up studies indicate that the lesions of fibrous dysplasia of bone may remain unchanged for many months or even years and that healing occurs following removal of the fibrous tissue. Recurrence was not noted in

any of our patients nor did sarcoma occur. The question of the frequency with which sarcoma develops in areas of fibrous dysplasia cannot be answered by our studies or by the material thus far reported in the literature. Coley and Stewart¹⁰ reported two cases of sarcoma in patients with fibrous dysplasia. However, microscopic sections from the lesions showed sarcoma from the outset. Jaffe²⁶ reported a patient in whom "an indubitable osteogenic sarcoma

TABLE V

Summary

Case	Age (yrs)		Sex	Race	Presenting Symptom	Skin	No of Bones Involved	Operative Treatment	Result	Length of Time Followed
	On-set	Admission								
1	5	5	M	W	Fracture of tibia and both femora	Cafe au-lait spots on back	20	a) Biopsy of fibula b) Neck exploration	Expired during neck exploration	
2	61	61	M	W	Pain in thigh	Normal	1	a) Biopsy of femur Curettage and phenol cauterization	Lesion filled in with dense bone symptom-free	13 yrs
3	25	25	M	C	Pain in chest	Small pigmented area on back	1	Excision of right 10th rib	Symptom-free	11 yrs
4	8	8	M	W	Fracture of femur	Normal	1	Curettage Bone chips inserted	Lesion filled in with dense bone symptom-free	10 yrs
5	6	13	F	C	Fracture of tibia	Normal	1	a) Curettage b) Exploration of neck	Lesion filled in with dense bone symptom-free	5 yrs
6	12	28	F	W	Pain in chest	Cafe-au-lait spots on back	5	a) Biopsy of rib b) Exploration of neck c) Excision of 8th rib	Improved	16 mos
7	25	33	M	C	Pain in chest	Depigmented area on back	3	Excision of right 10th rib	Symptom free	12 mos

developed in the tibia, which latter still showed evidence of fibrous dysplasia." Up to the time of writing, no report has appeared in which it was stated that exploration revealed fibrous dysplasia and subsequent exploration showed sarcoma.

SUMMARY

The clinical, laboratory, roentgenologic, operative and pathologic manifestations of seven cases and the follow-up studies on six cases of fibrous dysplasia of bone have been presented.

CONCLUSIONS

1. By no one study, that is, clinical, roentgenologic, operative, or pathologic, is it always possible to differentiate fibrous dysplasia from bone cysts and giant-cell tumors.

2 Fibrous dysplasia of bone can be differentiated from other diseases of bone by proper interpretation of the clinical, laboratory, roentgenologic, operative, and pathologic findings

3 In most instances of multiple bone involvement by fibrous dysplasia, the diagnosis can be made upon the basis of the roentgenologic findings and the calcium and phosphorus levels

4 Following fracture, healing usually occurs in fibrous dysplasia just as it does in bones in which there are cysts

5 In long bones, healing with new bone formation occurs following curettage

6 In a patient with fibrous dysplasia of a rib, if the lesion is accompanied by pain, the rib and intercostal nerve should be excised

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CARCINOMA OF THE LOWER LIP*

A TEN YEAR SURVEY

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DIVERSITY OF OPINION EXISTS in the literature as to the manner of treatment of carcinoma of the lip. The pros and cons of prophylactic neck dissection have been reported by Kennedy¹ and McClure². We shall not add to the arguments in this presentation but simply review the cases of epitheliomata of the lower lip which have come to operation, and the follow-up results obtained on the Tumor Division of the New York Post-Graduate Hospital.

The difficulty in evaluating the various forms of treatment of this condition is due in part to the inadequate and incomplete follow-up in this type of patient. In addition, the life expectancy of patients in this age group is lessened by the high incidence of intercurrent diseases.

Kennedy³ has described the routine followed at this clinic for management of carcinoma of the lip. In general, in patients treated since 1938, this pattern has been followed. A review of these cases, numbering 119, which were operated upon follows.

Of these 119 cases of carcinoma of the lower lip, four were found in women. The age distribution is shown in Figure 1. There was one case in a man 23 years old. Sixty-one per cent occurred in the sixth and seventh decade of life.

The duration of the lesion as stated in 114 cases is as follows:

1 mo	6	4 mos	10	7 mos	6	10 mo -1 yr	8
2 mos	11	5 mos	4	8 mos	4	1 yr -2 yrs	17
3 mos	17	6 mos	13	9 mos	4	Over 2 yrs	14

One half of the cases presented themselves before six months, and fully one third of the lesions were at least ten months in duration.

The pathologic diagnosis in all 119 cases was squamous cell carcinoma, 79 were of grade I, 14 of grade II, and five of grade III. Twenty-one were not graded. In only nine cases was the lesion larger than 3 cm. There was no correlation between length of history and size of the lesion, and the duration of these nine cases was well under nine months. There was no relationship between size and grade, and four of the five grade III lesions had lymph node metastases.

Cervical node specimens were obtained in 95 of the cases. Of 58 patients in whom nodes were palpable, involvement was found by microscopic section in 14 cases. In the remainder of the nodes a diagnosis of chronic lymphadenitis was made. Complete regression of epidermoid carcinoma metastases

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in cervical nodes from external radiation alone has been reported by some authors. In light of the above findings and similar findings in other series, and since it is impossible clinically to differentiate for certain a metastatic node from an inflammatory one, *the results of radiation must remain inconclusive unless nodes are removed*.

Four cases of positive node involvement were found in which nodes were not palpable preoperatively. Thus, absence of palpable nodes does not mean

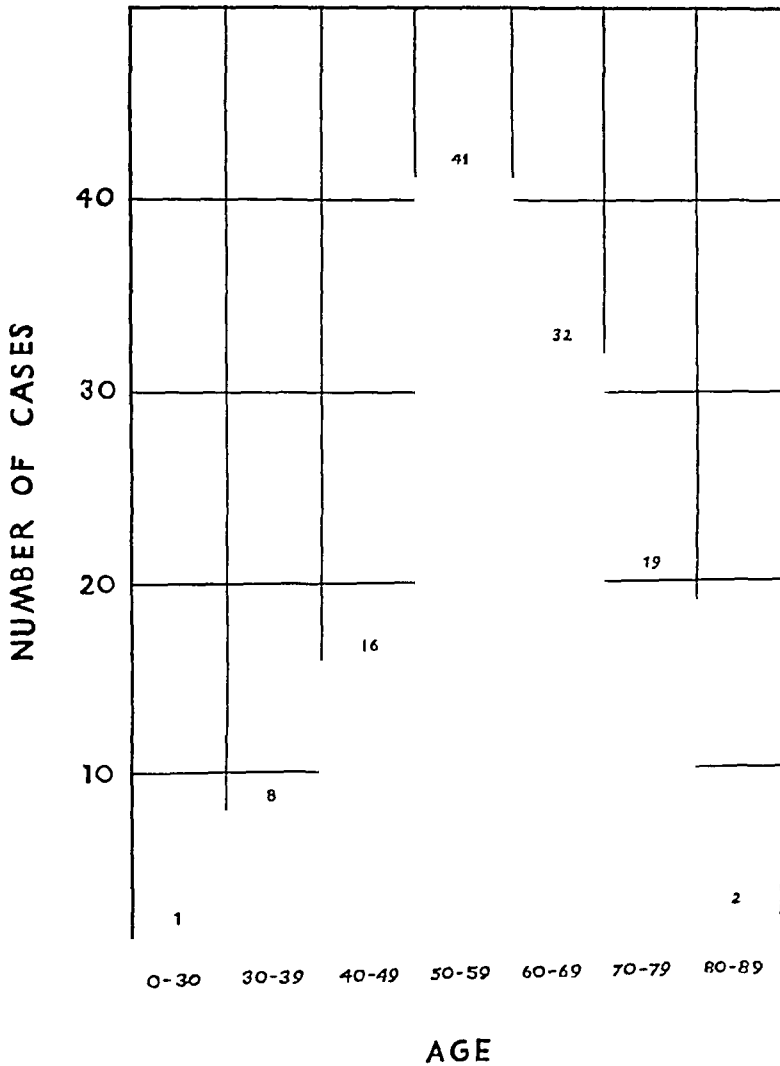


FIG 1—Age distribution

absence of metastases. Kennedy³ has pointed out previously that the absence of pathologic evidence of metastases does not necessarily mean absence of metastases. In general we agree that it is impossible to decide whether an enlarged node is involved or not, and certainly involvement may occur without palpable enlargement. In light of this, it is debatable whether frequent follow-up examinations offer assurance to the patient as to the time operative incision of the drainage area is indicated.

The surgical procedures used in these patients are as follows

Local excision alone	24
Local excision plus suprahyoid neck dissection (5 of these had further neck dissections)	79
Local excision plus omohyoid neck dissection (1 of these had further neck dissection)	14
Local excision plus complete neck dissection unilateral	1
'Commando' type operation with partial resection of lower jaw	1

LOCAL EXCISION

Local excision alone was performed on 24 patients. The operation was usually a "V" excision (19 cases) but, when the growth was large, adequate excision plus plastic repair was performed (five cases).

In one instance a local excision alone was performed for palliation in a far advanced case with metastases to the lung. This patient expired one month later. It was planned to do a prophylactic neck dissection in the remaining 23 cases, as is the policy at this clinic, but these patients either refused further operation or failed to return for additional operative procedure.

The follow-up results in these 23 cases is as follows

(a) Alive and well	16
(b) Alive with possible metastases present lost to follow-up	2
(c) Dead of undetermined cause	3
(d) No follow up	2

(a) Fifteen of the 16 patients who were alive and well at the last follow-up visit had no evidence of recurrence for the following length of time

9 yrs	1 case	3 yrs	4 cases
6 yrs	1 case	2 yrs	3 cases
4 yrs	1 case	½ yr	5 cases

The other patient developed local recurrence two years later. The lesion was re-excised two years after that and the patient was followed for an additional year without evidence of recurrence, local or otherwise. It is noteworthy that in all but two of these 16 patients who were alive and well at the last follow-up, there were no palpable nodes preoperatively. The two patients with palpable nodes in the submaxillary region were among those who were followed for the one-half year period only.

(b) Two patients developed large palpable masses in the neck six months following excision but failed to return for further treatment. These two patients had palpable nodes preoperatively.

(c) Three patients died two years, six months, and three months respectively postoperatively from undetermined causes. There was no evidence of recurrence of carcinoma in that time.

(d) In two cases there was no follow-up. These had palpable nodes.

In this group of 23 cases in which local excision was done preliminary to intended prophylactic neck dissection it is interesting to note the follow-up in the seven cases of the group who had palpable nodes. Of the five who were followed, one died three months later from undetermined cause, two were those who developed cervical masses six months later and two had no evidence of enlargement six months following excision.

No definite conclusions can be drawn from the material available in this group. Certainly patients with enlarged nodes should have definitive treatment instituted to eradicate possible cervical node involvement.

LOCAL EXCISION PLUS SUPRAHYOID NECK DISSECTION

Seventy-nine cases had local excision plus suprahyoid neck dissection, 66 of these at one operation. In the majority of instances the neck dissections were performed bilaterally. Aside from the fact that many of the lesions occur in the middle one-third, in which cases a bilateral dissection is indicated, we feel that a better cosmetic result can be obtained if the dissection is carried out on both sides. In 12 cases positive evidence of metastases in the nodes was found, and in five of these additional cervical node dissection was done. There were no operative deaths.

In the 67 cases with negative nodes, follow-up was available in 64 cases; 59 had no recurrence in the time followed as indicated below:

9 yr	2	4 yr	5
8 yr	4	3 yr	11
7 yr	2	2 yr	10
6 yr	6	1 yr	8
5 yr	6	½ yr	5

One patient died one year later, presumably from carcinoma. Four patients died from causes other than carcinoma. Two of the latter lived six years and five years respectively postoperatively, and had no evidence of recurrence.

In the 12 cases with positive nodes, five underwent further surgical procedures:

Further Procedure	Nodes	Follow Up	
Right omohyoid	Negative	5 years	no recurrence
Bilateral omohyoid	Negative	Died 2 yr	cause undetermined
Left omohyoid	Positive	Died 6 yr	carcinoma
Left complete	All nodes positive	Died 1½ yr	cause undetermined
Bilateral complete	All nodes positive	Died ½ yr	cause undetermined

Seven cases had no further surgery. Of five cases followed, four lived three years without recurrence, and one died one and one-half years later after receiving roentgen ray treatment as a palliative measure.

Of five patients with positive nodes removed in suprahyoid dissection in whom further surgery was done, three were found to have positive nodes below the suprahyoid region. The prognosis in all cases where suprahyoid nodes are found involved is poor. In ten cases followed, only six patients were alive after three years. One of these died at six years. It would seem that the time margin of safety is small once nodes are involved. In 64 cases followed for varying periods after suprahyoid neck dissection and in whom nodes were negative, there was only one known death from carcinoma occurring one year postoperatively.

LOCAL EXCISION PLUS OMOHYOID NECK DISSECTION

Local excision plus resection of nodes above the omohyoid crossing was performed in 14 patients. One required additional cervical node dissection. There were no operative deaths.

In ten of these cases, the excised nodes were negative for metastases. Six of these patients had palpable nodes on physical examination. In the follow-up of these patients there was no known recurrence of the carcinoma. Nine were followed for variable times as shown:

9 yr	3	2 yr	2
4 yr	1	1 yr	2
3 yr	1		

Four of the 14 cases had positive nodes. Three were limited to nodes in the suprahyoid region of the neck. One of these was followed ten years and one was followed four years without evidence of recurrence. The third case, a lesion of grade II, developed a recurrence in the neck one year postoperatively, had further neck dissection to the clavicle, and died one year later.

In one case of initial omohyoid dissection all the nodes removed above and below the level of the hyoid bone were found to be involved. This patient developed a large cauliflower mass in the neck six months later and no further follow-up was obtained. This lesion was of grade III.

There is no evidence of recurrence of carcinoma in those cases in which prophylactic omohyoid neck dissection was done and negative nodes were found. Two of the four cases with positive nodes undoubtedly died of the carcinoma. These lesions were of a more malignant variety as indicated by the grade.

One patient, age 75, had a local excision plus unilateral complete neck dissection. The tumor was found to involve all the nodes of the neck that were removed and extended to the adventitia of the internal jugular vein. This patient died on the first postoperative day from pulmonary edema. This was the only operative death in the entire series.

Another extensive case required a partial resection of the right mandible, together with a complete neck dissection. This patient lived only six months following the operation.

SUMMARY

1 A review of 119 cases of carcinoma of the lower lip treated surgically at this clinic since 1938 is presented.

2 Neck dissections of various magnitudes were done in 95 of these cases in conformity to the routine here. There was one operative death in a man 75 years of age who had extensive involvement and in whom a complete unilateral neck dissection was done.

3 Nodes were found positive for malignancy in 18 of the 95 cases in whom cervical node dissections were done. In 77 cases, the nodes were found free of malignancy on microscopic examination. The follow-up results in these 2 groups of patients is as follows:

	Negative Nodes (77)	Positive Nodes (18)
Well for 5 years	25	2
Follow up for less than 5 years and well	47	5
Died of carcinoma	1	5
Dead from cause undetermined	0	4
Lost to follow-up	4	2

CARCINOMA OF THE LOWER LIP

There was one known death from carcinoma among those cases in whom nodes were removed and found histologically negative for metastases. The prognosis in these cases is good. Once the regional nodes are involved, the prognosis as judged from available follow-up becomes much worse in spite of radical neck dissections. When nodes become initially involved, the time factor of safety seems to be small, since further node group involvement is the rule.

4 In light of the extremely low mortality of neck dissections, the uniformly good results obtained in available follow-up when nodes removed were found to be negative, and the relatively poor results obtained once nodes are involved, it would seem that prophylactic neck dissection in cases of carcinoma of the lip is strongly indicated.

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PRIMARY CARCINOMA OF THE URETER*

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WHILE PRIMARY CARCINOMA OF THE URETER is not a common tumor, it no longer can be regarded as rare. In 1934, Lazarus¹² was able to collect only 68 cases from the literature of the preceding 90 years. Nine years later, however, Scott¹⁹ found 182 and Sauer¹⁸ 189. In 1948, Gulatieri, Hayes and Segal⁹ collected 196 cases and added two of their own. We wish to report seven additional cases.

CASE REPORTS

Case 1—C H, Record No 24259, a 59-year-old white male, was admitted on September 9, 1936, because of hematuria. The patient had his first attack of gross hematuria in 1934. This stopped in one day under bromide and citrate therapy. No further bleeding occurred until two months prior to admission, when it again responded within a day to the same therapy. Cystoscopy done at that time revealed inflammation of the right ureteral orifice, obstruction of the ureter 4 cm above the orifice, and a non-functioning kidney. On both occasions there was gross bleeding accompanied by clots but no pain. For the past 25 years the patient had occasional attacks of gnawing pain in the right lower quadrant which had been diagnosed as chronic appendicitis.

Physical examination was entirely normal. B P 140/80. Urinalysis was negative except for a trace of albumin. Hb 85 per cent, rbc 4.5 million, Wbc 7,200, BUN 15. A chest roentgenogram was not remarkable.

A diagnosis was made of neoplasm of the right kidney. On September 10, a transperitoneal right nephrectomy and appendectomy were done. The right kidney contained 500 to 600 cc of clear urine. The ureter passed through a rough, hard, egg-sized mass which involved the appendix. The mass, appendix, and kidney were removed.

Pathology report "Gross. The kidney is hydronephrotic. The ureter is surrounded by a 6 by 6 by 3 cm firm, fairly well encapsulated mass involving the tip of the appendix. Microscopic. The bulk of the tumor consists of fibrous stroma which surrounds sheets and strands of epithelial cells, most of which are polyhedral and tightly packed. Scattered cells are large and round, sometimes bizarre, and frequently show kerato-hyaline granules and abortive pearl formation. The appendiceal wall has been infiltrated by tumor cells but the lumen is obliterated by fibro-adipose tissue. The ureter is recognized by the remnants of the smooth muscle of its wall. Lymphatic permeation is noted. Diagnosis. Moderately undifferentiated squamous cell carcinoma of the ureter (Carcinoma, grade III), hydronephrosis."

The postoperative course was complicated by right thrombophlebitis. The patient was given a course of deep roentgen ray therapy and discharged October 2, 1936.

C H was re-admitted on January 10, 1937, complaining of weakness (three months duration), anorexia (two months), constipation (two months), and fecal vomiting (12 to 14 hours).

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Positive findings on physical examination were as follows T 99°F B P 150/90 The abdomen was distended and tympanitic There was a hard, fixed, plum-sized mass on the right, midway between the umbilicus and anterior superior iliac spine Another hard mass, slightly larger, was present just below and slightly to the right of the navel The right leg was swollen and slightly tender

Urinalysis was negative Hb 80 per cent, rbc 3.8 million BUN 37

On January 11 a laparotomy was done Hard masses were present in the abdominal wall, the veins of which were engorged A hard fibrous mass was adherent to the spine and lower ileum The liver was studded with nodules The ileum was anastomosed to the colon near the hepatic flexure and an ileostomy done The patient was given additional deep roentgen ray therapy and discharged February 1 The patient died at home on March 4, 1937, of generalized carcinomatosis An autopsy was not performed

Comment This case illustrates the fact that the hematuria associated with these cases may stop for weeks or months under non-specific treatment Frequently this results in delaying adequate study of the patient This case was unusual in that the carcinoma of the ureter involved the appendix and later caused intestinal obstruction

Case 2—N B M, Record No 30744, a 58-year-old white female, was admitted on June 29, 1937, because of hematuria The patient had first noticed hematuria associated with frequency and nocturia in 1935 She was admitted to Temple University Hospital A letter from Dr W Wayne Babcock stated that on October 22, 1935, the right ureter just below the renal pelvis had been resected because of a papillary tumor 1 cm in diameter The ureter was re-anastomosed to the pelvis with wire sutures

Review of a slide kindly sent to us by Dr Ernest E Aegerter showed a papillary transitional cell carcinoma showing occasional mitotic figures and little tendency to invasion, which we interpreted as papillary carcinoma, grade I

In the early part of 1937 the patient again noticed hematuria She entered this hospital for a nephrectomy Past history revealed that a vaginal hysterectomy had been done in 1929, because of a suppurating cystadenocarcinoma of the right ovary At that time the specimen showed no microscopic evidence of the ovarian tumor penetrating the peritoneum

Except for old rheumatic heart disease, physical examination was negative B P 110/80 Urinalysis disclosed marked albuminuria, many pus cells, and occasional red cells A diagnosis of pyelonephritis secondary to postoperative uretero-pelvic stricture was made

On June 30, 1937, a right nephrectomy was done, and the patient was discharged on July 21, 1937

Pathology report "Gross The kidney weighs 85 Gm and displays a narrow cortex The region from which the tumor is said to have been removed at a previous operation shows nothing unusual Microscopic Section through the region from which a tumor had previously been removed does not show any malignant change The medulla and cortex show areas of polymorphonuclear infiltration and in one area there is a small abscess Diagnosis Acute suppurative nephritis"

The patient was re-admitted on January 12 1943 Six months after her nephrectomy in 1937, she began to have hematuria Cystoscopy revealed papillomata of the bladder which were fulgurated Thereafter the patient had recurrences of hematuria and papillomata requiring fulguration every 3 to 4 months

In November, 1942, she began having attacks of weakness The hematuria had become almost constant but did not consist of bright red blood or clots She complained of generalized aching, upper abdominal pain, dyspnea, and palpitation There had been a weight loss of 15 to 25 lbs in the past 6 months

Physical examination differed from the previous one as follows B P 172/112 The liver was 3 finger-breadths below the costal margin and was hard, nodular and nontender There were no other palpable masses

Urinalysis was negative Hb 13 Gm , rbc 4.4 million Wbc 13,600 , N 76 per cent, E 8 per cent, L 16 per cent Sedimentation rate 94 BUN 16 Liver function tests were within normal limits

Roentgenograms of the chest and abdomen revealed no metastasis to the spine Barium enema revealed displacement of the colon by the large liver

On February 3 an exploratory laparotomy was done Nodules were present in the liver and retro-peritoneal lymph nodes On the right side, occupying the region of the ureter, there was a sausage-like, hard, nodular mass extending from the level of the umbilicus down into the pelvis Cystoscopy showed multiple papillomata of the bladder

The patient gradually went downhill On February 27 she had marked oliguria due either to obstruction or a hepato-renal syndrome She died March 1, 1943 Autopsy diagnosis was as follows Transitional cell carcinoma, moderately undifferentiated of ureter, metastatic in retroperitoneal lymph nodes, liver, mesentery, and lungs

Comment Although all of the involved ureter was supposedly excised in 1935, the patient developed papillomata of the bladder and stump of ureter This points towards a multi-centric origin of these tumors

Case 3—W E, a 63-year-old white male was first seen at the Urologic Clinic on November 10, 1938, with a chief complaint of hematuria Painless intermittent hematuria had started two months prior to admission Physical examination was essentially negative

Cystoscopy on November 10 revealed a pedunculated 3 cm growth in the vicinity of the left ureteral orifice The tumor was electro-coagulated The base was again fulgurated on November 17

Cystoscopy on January 27, 1939, revealed a small papillary growth around the left ureteral orifice and two small papillomata above and to the left of this orifice These were fulgurated Numbers 5 and 6F catheters met an obstruction at 9 cm up the left ureter An attempt was made to do a retrograde pyelogram but no radio-opaque medium could be visualized on the left side An excretory urogram disclosed a non-functioning left kidney Another retrograde pyelogram was attempted on January 28 without success

Cystoscopy on May 9, 1939, demonstrated 12 ounces of residual urine There were two papillomata, each about 1 cm in diameter, around the left ureteral orifice The entire vesical neck was the site of papillary growths These had extended into the prostatic urethra

On June 9 a suprapubic cystotomy was done Multiple growths covered the vesical neck, trigone and prostatic urethra The right ureteral orifice was not involved and spurted clear urine The left ureter was split upward and the lower portion found filled with papillomata All the growths were fulgurated

Pathology report "Gross Specimen consists of three small masses of soft, lobulated brown tissue Microscopic Protruding from the bladder mucosa are papillary stalks of various diameters which bear masses of moderately undifferentiated transitional type epithelium The latter shows moderate mitotic activity, with occasional atypical figures, and a distinct tendency to infiltrate underlying structures Diagnosis Moderately undifferentiated transitional cell carcinoma of bladder (Papillary carcinoma, grade III)

On June 26 a left nephrectomy was done The kidney was markedly adherent The ureter, four times normal in size, was severe, below the pelvic brim

Pathology report "Gross The 8 by 5 by 3 cm kidney has a mottled surface and is hydronephrotic Two pyramids are thickened by firm, white, partially encapsulated

tissue In four-fifths of its length, the ureteral mucosa and muscularis are both apparently involved by soft, granular, white tissue Microscopic Sections of the kidney show nodules of rather undifferentiated transitional cell epithelium Small fragments of the latter are seen in lymphatic channels Other areas of the kidney show marked infiltration by lymphocytes, plasma cells, and eosinophiles The ureter is lined by neoplastic epithelium similar to that of the bladder although the invasiveness of this tumor is less marked Diagnosis Moderately differentiated transitional cell carcinoma of ureter (Papillary carcinoma, grade III) Transitional cell carcinoma, metastatic, of kidney Hydronephrosis and pyelonephritis

A chest film on October 4 revealed bilateral pulmonary metastases The patient died on November 2, 1939

Comment In all cases of bladder papillomata, the upper urinary tract should be studied This is especially true if a ureteral orifice is involved Obstruction to the passage of a catheter is one diagnostic sign indicating involvement of the ureter

Case 4—Z G, Record No 63606, a 60-year-old white male, was admitted on December 29, 1941, with a chief complaint of low back pain of five months duration The pain was most prominent over the coccyx and worse upon walking

Physical examination revealed the following B P 190/110 The liver edge was just palpable The prostate was moderately enlarged and non-nodular Reflexes were sluggish in the lower extremities but no pathological reflexes were present

Urinalysis was negative except for 2 plus albuminuria Hb 14.1 Gm, rbc 4.1 million Wbc 7,400, N 75 per cent, E 1 per cent, L 23 per cent, M 1 per cent Sedimentation rate 44 mm/hr BUN 14 Acid phosphatase 173 Gutman units Serology negative Lumbar puncture revealed both pressure and spinal fluid to be normal

A urological consultation disclosed the following Frequency, burning, dribbling, difficulty in starting the stream, and nocturia 2X of five months duration During this same period, the patient suffered severe sharp, constant low back pain A transurethral resection had been done on November 24, 1941, with some relief of symptoms Prostate, grade I, enlarged, firm and smooth There was no tenderness on manipulating the prostate or coccyx Prostatic secretions were loaded with pus cells A stricture was present just inside the meatus This was dilated from 12 to 20F and cystoscopy done Two ounces of residual urine were present There was some enlargement of both lateral lobes with anterior notching and a slight median bar Indigocarmine appeared in 5 minutes from the right ureteral orifice but none from the left A 6F catheter was passed 27 cm on the right No catheter could be passed beyond 3 cm on the left

Roentgenograms of the chest and abdomen revealed no evidence of metastasis Osteoarthritic changes were present at the apophyseal joints between L3 and 4 Retrograde pyelogram showed a somewhat irritable right kidney consistent with chronic pyelonephritis No radio-opaque medium was present on the left side An excretory urogram demonstrated less irritability than previously on the right and no function on the left Diagnosis Tumor of left ureter with secondary hydronephrosis

Sigmoidoscopy and barium enema were negative The orthopedic consultant believed the pain was of neurological origin On February 11, 1942, a left nephro-ureterectomy was done

Pathology report "Gross The kidney is hydronephrotic The ureter is dilated as far as a mass palpable in its lower end After opening the ureter a firm, irregular, grayish-white tumor mass 4 by 1.5 cm is seen to arise from the mucosa Microscopic The ureter apart from the tumor proper, is lined by transitional epithelium showing neoplastic

change, the cells being hyperchromatic and forming a pseudostratified structure. The tumor above this grows into the lumen and completely obliterates it. There is rich invasion of lymphatic and venous channels. Diagnosis: Moderately undifferentiated transitional cell carcinoma of ureter (Papillary carcinoma, grade III)."

Postoperatively the patient continued to have coccygeal pain. Roentgen ray of the chest, pelvis and upper femora revealed no metastasis. Injection of the 3 left sacral foramina with procaine relieved the pain temporarily. Injections of ammonium sulfate were given with relief of pain. He was also given a full course of deep roentgen ray therapy. The patient was discharged March 30, 1942.

He was re-admitted on May 10, 1942, because of continued back pain which radiated down the left leg. Otherwise his general condition seemed good. Physical examination was the same as previously with the following exceptions: B P 200/110. Pain was present over L3, 4, S1, 2, 3, and C1. There were no changes in heat, cold or position sensation. No pathological reflexes were present. Urinalysis was negative. Hb 7.8 Gm, rbc 2.6 million, Wbc 9,900, N 66 per cent, L 34 per cent, BUN 9.

Following a bilateral chordotomy on May 11, the patient developed paralysis of the lower extremities and loss of sphincter control. He was discharged on October 31, 1942, and died four months later.

Comment This case indicates that pain from tumor metastases may be one of the first symptoms. Though the tumor may grow slowly locally, it frequently penetrates the thin ureteral wall early. Probably the urinary symptoms were partially due to a secondary chronic pyelonephritis as a result of obstruction by the ureteral tumor as well as the prostate.

Case 5—G O, Record No 93893, a 64-year-old white female was admitted on April 29, 1946, because of progressive hematuria of one year's duration. For a number of years the patient had a dull ache just above the left iliac crest. The urinary stream seemed smaller in the past 6 months. There was some burning and occasional nocturia.

Physical examination was normal except for some induration of the right vaginal wall but none on the left. B P 135/70. Urinalysis disclosed 2 plus albuminuria, occasional granular casts, and many pus and red cells. Hb 14 Gm, rbc 4.0 million, Wbc 9,500, N 76 per cent, L 22 per cent, M 2 per cent, BUN 14.

Cystoscopy revealed a broad based papillary growth involving the entire right quadrant of the bladder but not the vesical neck. The ureteral orifices could not be seen. A flat plate of the abdomen disclosed a normal left kidney but the right was enlarged and seemed partially obscured by an associated soft tissue mass. Upon excretory urography a normal left kidney was visualized but the right was non-functioning. A medium-sized lobulated mass of polypoid type occupied the right half of the bladder. Cholecystography demonstrated a normal gallbladder which was not connected with the right kidney.

On May 8 a suprapubic cystotomy was done. A cauliflower-like mass was attached to both the outside and inside of the right ureteral orifice. The mass was fulgurated. An elliptical incision was made around the orifice and the ureter freed. The growth was felt to end 2 inches above the orifice. The ureter was excised three quarters of an inch above the growth and re-implanted in the bladder.

Pathology report "Gross: The specimen is a soft, cauliflowerlike piece of reddish-brown tissue. Microscopic: The tissue consists of arborizing papillae with slender vascularized stalks surmounted by moderately well-differentiated papillary transitional epithelium. Diagnosis: Moderately well differentiated papillary transitional cell carcinoma of ureter (Carcinoma, Grade II)."

The patient made an uneventful postoperative recovery. An excretory urogram on May 31 visualized a normal left kidney. Dye first appeared in 25 minutes on the right.

In 60 minutes a large right hydronephrosis and hydroureter were demonstrated. The bladder appeared normal. The patient was discharged from the hospital on June 3, 1946.

She was seen at two month intervals at the clinic. The patient remained well until October 25, 1946, when many pus cells with occasional red cells were found. Cystoscopy disclosed a normal bladder. Right kidney and bladder urine showed no pus cells and occasional red cells. Both specimens grew proteus organisms on culture. The last clinic visit of the patient was in January, 1947, at which time she felt well and had no complaints. In a telephone conversation in February, 1949, the patient stated that for the past month she had been losing weight, tired easily and was pale. However she did not wish to be cystoscoped.

Comment Tumor seen protruding from an orifice is pathognomonic of carcinoma of the ureter or renal pelvis. Occasionally conservative surgery may be curative. It is always indicated where the involved kidney is necessary to sustain life.

Case 6—A. M. S., Record No. 56355, a 64-year-old white male was admitted on July 1, 1948, because of hematuria. Four days prior to admission the patient had gross hematuria with the passage of clots. This cleared toward evening and recurred the following morning. During the past week the patient had some difficulty in starting his stream and it was slightly diminished in size.

Positive physical findings were as follows: B. P. 165/95. The prostate was Grade I enlarged, soft and non-nodular. Urinalysis was negative except for 1 plus albuminuria. Hb. 16 Gm., rbc 4.7 million, Wbc 8,500, N 64 per cent, E 5 per cent, B 1 per cent, L 27 per cent, M 2 per cent. BUN 24.

Cystoscopy demonstrated 4 ounces residual urine. The bladder mucosa was markedly trabeculated and the trigone congested. The posterior urethra was injected and bled easily. The lateral prostatic lobes were grade II in size with anterior notching, and moderate middle lobe enlargement. Indigocarmine appeared in 5 minutes from the right ureteral orifice but none in 15 minutes from the left. A 6F catheter passed 27 cm. with ease on the right. An obstruction was met at 15 cm. on the left which was passed with slight difficulty. Six cc. of radio-opaque medium filled the right pelvis and 14 cc. the left.

Retrograde pyelography disclosed a normal right kidney and ureter. There was marked hydronephrosis and hydroureter on the left. At the level of L4, a filling defect was seen in the ureter. The ureter below this defect appeared normal. A chest film showed no evidence of metastasis.

Cystoscopy was repeated on July 20. Bladder findings were the same. A catheter met an obstruction at 15 cm. which could not be passed. A diagnosis of left ureteral tumor was made.

On July 26 a left nephrectomy and partial ureterectomy were done. The ureter was twice normal size. At the junction of the middle and lower thirds, a small stone-like pebble was felt within the ureter. Immediately below this a soft mass was present. This portion of ureter had marked periureteritis. Below the mass the ureter was normal in size. The ureter was severed 1 inch below the mass.

Pathology report "Gross: The kidney is hydronephrotic. An 8 cm. section of ureter exhibits a 2 by 1 cm. tumor 1 cm. from the distal end. Microscopic: Cross-section of the ureter shows the lumen to be almost completely occluded by an ingrowth from the lining. The neoplasm forms broad folds composed of layers of large, fairly sharply defined, irregularly shaped cells presenting numerous hyperchromatic nuclei and several atypical mitotic figures. A small lymphatic capillary in the ureteral wall is plugged with a mass of the malignant tumor. The kidney shows chronic inflammation. Diagnosis: Moderately

due to pressure on the sacral plexus. Of the textbook triad, pain, hematuria and mass, the last is least common, being found in about 45 per cent of the cases. The mass palpated is usually the hydronephrotic kidney. Only rarely, as in the case of a well developed tumor, can the actual carcinoma be felt. Butler,² and Paschkis and Pleschner¹⁶ have reported palpation of these tumors rectally and vaginally.

According to Edelstein and Marcus,⁴ urinary frequency occasionally occurs, especially if the tumor is in the lower third of the ureter, which was the case in 60 per cent of those reported by Vest. The hydronephrotic kidney may become secondarily infected, leading to symptoms of pyelonephritis, acute or chronic, pyonephrosis, or perinephric abscess.

Scott states that the correct preoperative diagnosis is made in less than 36 per cent of the cases. In approximately 30 per cent, blood can be seen coming from the ureteral orifice of the involved side. Papillary excrescences protrude from the orifice in 25 to 30 per cent of the cases. Ureteral obstruction upon catheterization is present in 50 to 60 per cent. Bleeding may follow manipulation of the catheter. Especially significant is obstruction to the passage of a catheter which occasions fresh bleeding followed by clear urine after the catheter has passed the obstruction.

The preoperative diagnosis has most often been made by the presence of a filling defect in the pyelo-ureterogram. This is not always successful where the tumor prevents the radio-opaque medium from ascending. Neuwirth and Bedina¹⁵ demonstrated the value of pneumo-pyeloureterography in these cases. Vest²⁰ states that a filling defect in roentgen ray occurs in only 15 per cent of cases. According to Kimball and Ferris,¹¹ it is important to remember that these ureteral tumors may arise from tumors of the renal pelvis.

Carcinoma may sometimes be diagnosed by the presence of exfoliated tumor cells in urine.

In Lazarus and Marks¹³ review, men were affected twice as frequently as women. The greatest incidence occurred in the fifth to sixth decade, although the range in Scott's¹⁹ series was from ages of 22 years to 89. The right ureter was involved over the left in a ratio of 3 to 2. In differential diagnosis, tumors of the kidney, bladder and prostate, tuberculosis, calculi, and ureteral stricture must be considered.

Treatment The most acceptable form of treatment, according to the literature, is an extraperitoneal nephro-ureterectomy with removal of a cuff of bladder. Excision of the tumor bearing area in the lower ureter with re-implantation of the ureter into the bladder is the commonest conservative procedure. Vest advocates the local removal of the ureteral tumor in those cases which are clinically and histologically believed to be benign, and in which loss of function of the involved side would prove immediately fatal. Deep roentgen-ray therapy has proved to be of little value so far as cure is concerned.

Most of the patients reported in the literature die within two years after operation. Because the ureter has a thin wall and an abundant blood and

lymphatic supply, metastases occur early. The commonest sites are in the retroperitoneal lymph nodes 30 per cent, liver 14 per cent, bones 12 per cent, lungs 5 per cent, and bladder 6 per cent.

Pathology In his review of 182 cases, Scott¹⁹ lists 22 categories into which these tumors have been placed. Since the pathological characteristics of all tumors of the urinary transitional epithelium (Melicow's urothelium) are similar, the grading system of the Registry of Bladder Tumors⁸ should be employed here. According to this system, Grade I comprises the papillomata with typical cells and no invasion of bladder or pedicle. Grade II includes tumors which are not uniform in cell arrangement or type and in which there may or may not be histologic evidence of invasion. Grade III are tumors showing infiltration, cellular atypism and considerable mitotic activity. Extremely anaplastic tumors are placed in Grade IV.

Most authors are inclined to regard all epithelial tumors of the genito-urinary tract as at least potentially malignant, although Vest²⁰ has collected a series of benign ureteral tumors. The Registry's experience with Grade I lesions of the bladder seems to be in agreement with this concept for such tumors have often progressed to frank carcinoma.

Due to the difficulty of diagnosis and the consequent delay of treatment, ureteral tumors often progress farther than those of the bladder. Behavior of all tumors of the urinary tract is extremely difficult to predict. In general, infiltrating tumors lead to earlier metastasis than non-infiltrating, although Grade I tumors may unexpectedly metastasize.

The cause of tumors of the urinary transitional epithelium is not known. It seems inescapable that some component of the blood or urine is at least partly responsible. Pearse's¹⁷ cases in which marked regression of bladder tumors followed ureteral transplants would seem to indict the urine, although Gay⁷ and Ferguson⁶ have favored a blood-borne agent.

There are certain circumstances which undoubtedly predispose to carcinoma. The outstanding instance is that of chronic exposure to aniline dyes either in industry or experiment. Willis²² believes that exstrophy of the bladder predisposes to carcinoma and that schistosomiasis might. He also believes that Brunn's nests and other forms of metaplasia predispose to adenocarcinoma. Bothe¹ found such changes in areas near ureteral tumors and thought that they were the precursors of frank tumor. Fagerstrom⁵ could find no correlation between epithelial budding and solid tumors of urinary epithelium. The question of chronic infection predisposing to carcinoma is difficult to assess and the recent literature does not emphasize it. Willis²² says that the first symptoms of bladder carcinoma are due to the tumor rather than other urinary disease.

SUMMARY

Seven cases of primary carcinoma of the ureter are reported. Hematuria, pain and mass, in that order, are the most common symptoms. The mass is usually a hydronephrosis secondary to obstruction by the tumor. Symptoms

may result from an infected hydronephrosis. Tumor seen protruding from a ureteral orifice is pathognomonic of carcinoma of the ureter or renal pelvis. A filling defect in the pyelo-ureterography is suggestive. Treatment should be radical. Conservative surgery is indicated where the involved kidney is necessary to sustain life. Most of these patients die within two years after the diagnosis has been made. A plea is made to follow the Registry of Bladder Tumors classification. The cause of these tumors is unknown. All are potentially malignant.

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ADDENDUM—THREE LATE CASES

Case 8—E. F. S., No. 107668. Right nephrectomy was done in 1947 because of hydronephrosis, re-admitted February, 1949, with burning and frequency. Cystoscopy revealed a papillary tumor surrounding R. U. O. Right ureterectomy including bladder cuff was done, with discharge April 19, 1949.

Pathology Report Transitional cell carcinoma, grade two, of the ureter.

Case 9—R. E. A., No. 21705. Admitted June, 1949, with hematuria nine months. Papilloma near left ureteral orifice fulgurated September, 1948. Several recurrences fulgurated. Left ureteronephrectomy was done, with excellent recovery.

Pathology Report Papillary transitional cell carcinoma, grade two, of ureter.

Case 10—A. B. Hematuria ten days. The tumor, protruding from the ureteral orifice, fulgurated elsewhere a week before. Excretory urogram revealed a lesion of the distal end of the right ureter. Nephroureterectomy was done, with recovery.

Pathology Report Transitional cell carcinoma, partially differentiated, of the right ureter.

ANEURYSM OF THE COMMON CAROTID ARTERY¹

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Aneurysm of the common carotid artery is a relatively uncommon lesion. During a 20-year period, from 1927 to 1947, this diagnosis was made only five times in the surgical service of the Hospital of the University of Pennsylvania. In Reid's review¹ of aneurysms treated at the Johns Hopkins Hospital only ten were found to involve the common carotid artery. In occasional reports during the past 15 years this lesion has been discussed and cases have been added to the literature.²⁻⁷ This is in contrast to aneurysm of the internal carotid artery which is relatively common.

At least 90 per cent of all aneurysms of the common carotid artery are due to syphilis.⁸ Hence, as this disease becomes more uncommon, this aneurysm will become increasingly rare. Most spontaneous aneurysms of the internal carotid artery, on the other hand, are now generally conceded to be congenital in origin.⁹ Traumatic aneurysms are usually due to gunshot wounds or stab wounds.

The treatment of common carotid aneurysms, particularly of spontaneous aneurysms, has been difficult and often disappointing. Reid¹ considered that only four of the ten reported by him were known to be cured. In using treatment radical enough to effect a cure, hemiplegia has been a constant threat. Recurrence has frequently followed the use of conservative methods, such as simple ligation. In some instances hemiplegia has occurred hours or days following an operation thought, at first, to be successful. Hemorrhage resulting from the erosion of bands or ligatures has been a serious complication. In general, six types of management have been recommended:

1 Do nothing. Some have considered the prognosis to be better without surgical treatment, particularly in patients over 50 years of age.

2 Proximal occlusion of the common carotid artery, with bands or ligatures.

3 Distal occlusion of the common or of the external and internal carotid arteries.

4 Proximal and distal occlusion, simultaneously or in stages.

5 Aneurysmorrhaphy, using any of the three classical methods of Matas.

6 Excision, following proximal and distal ligation.

Small aneurysms have been cured by methods 2, 3, and 4, but these methods have not been successful in curing large aneurysms, even though pulsations were at first obliterated. The fifth method, aneurysmorrhaphy, has been applicable and successful for some traumatic aneurysms but has been

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infrequently used for spontaneous aneurysms because of the difficulty of suturing vessel walls, the site of advanced degenerative disease. Excision, when not followed by complications, has given excellent results and has been curative.

The major problem in treating these lesions has been the danger of hemiplegia resulting from ligation of the carotid arteries. The incidence of cerebral complications following carotid ligation cannot be stated with certainty because of the many variable factors involved. Pilcher and Thuss,¹⁰ in an extensive review of the world literature, concluded that cerebral complications occur in 20 to 30 per cent. Watson and Silverstone¹¹ reported cerebral complications in 70 per cent and a mortality of 50 per cent following carotid ligations in patients with cancer of the head and neck. These figures are probably higher than average because of the age and debility of many of their patients. Freeman¹² reported cerebral complications in 20 to 25 per cent and Matas¹³ a mortality of 12 per cent following ligation of the common carotid artery. Lahey and Warren¹⁴ considered the risk of carotid ligation too great to be warranted during excision of carotid body tumors.

Various methods of testing and of increasing the adequacy of collateral circulation have been proposed to reduce the incidence of cerebral complications. These have been discussed by Matas,¹⁵ Dandy,¹⁶ Schorstein,¹⁷ Olivecrona,¹⁸ Dorrance,¹⁹ Jefferson,²⁰ Sweet and Bennett,²¹ and others. The methods commonly used have been

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a Stimulation of the carotid sinus may cause syncope and other cerebral symptoms, with resultant confusion in the interpretation of the test.

b Sudden occlusion of a carotid artery may cause hemiplegia.²²

c The test is not always reliable, hemiplegia sometimes follows carotid ligation when adequate collateral circulation appears to be present.^{14, 18}

d It is difficult to be certain that the carotid artery is completely occluded by digital pressure, as demonstrated in the recent experiment of Sweet and Bennett.²¹

2 Occlusion of the carotid artery, exposed under local anesthesia for 3 minutes or more. This variation of the Matas test has been used to eliminate any doubt that the artery is completely occluded. Hemiplegia has followed hours or days later in some in whom this test was negative. Dandy¹⁶ believed that a propagating thrombus or an embolus accounted for such a complication while Schorstein¹⁷ presented evidence that it may be due to the delayed effect of ischemia, present at the time of ligation, but not becoming clinically apparent except as a result of a prolonged, cumulative effect.

3 Partial occlusion by constricting metal or fascial bands for one to six weeks to promote the development of adequate collateral circulation. This method was used particularly by Dandy,⁹ who considered it a satisfactory solution to the problem because of the rapid development of collateral circulation in response to this stimulus. In Dandy's experience it was rarely necessary to remove a band if care was taken to produce no more than 50 per cent occlusion of the artery, and excellent protection was afforded to the patient when ligation was finally performed. Dandy emphasized that the development of collateral circulation was unlikely in some individuals because of the presence of congenital anomalies of the Circle of Willis. These individuals could be eliminated, he believed, by the development of cerebral symptoms within ten minutes following digital occlusion of the carotid artery.

4 Active bleeding from the distal end of the vessel. This is an old method, used frequently by Halsted.¹ Actual spurting from the distal end of the artery has proved to be reliable evidence that the collateral circulation is adequate.

Using a sensitive manometer, Sweet and Bennett²¹ have recently studied the collateral circulation of the carotid arteries by measuring the pressure in the internal carotid artery during occlusion of the common carotid, common and external carotid, and both common carotid arteries. Their results have led them to propose this procedure as a method for testing the adequacy of the collateral circulation. In patients who withstood common carotid occlusion well the systolic pressure fell to 50 per cent and the pulse pressure to 25 per cent of its original level, demonstrating that carotid ligation for intracranial aneurysm reduces intra-aneurysmal pressure and, presumably, aids in thrombus formation. This technic was used to test the thesis that ligation of the common carotid is safer than ligation of the internal carotid artery, as contended by Dorrance,¹⁹ Schoenstein,¹⁷ and Olivecrona,¹⁸ because of collateral circulation passing from the opposite carotid artery through the external and into the internal carotid artery of the same side. The pressure recordings indicated that significant retrograde flow from the external to the internal carotid artery did not occur when the common carotid artery only was occluded. They concluded that, in elective procedures, the internal carotid should be ligated, as practiced by Dandy,⁹ rather than the common carotid artery. Finally, there was no evidence in their studies that the circulation was improved, following occlusion of the carotid arteries, by simultaneous occlusion of the internal jugular vein.

An unusually large luetic aneurysm of the common carotid artery was recently treated successfully at the Hospital of the University of Pennsylvania by excision. Preoperatively it was planned to use a vein or arterial graft if the collateral circulation appeared inadequate.

CASE REPORT

A M., a 61-year-old man, was admitted to the Hospital of the University of Pennsylvania on April 30, 1948. In November, 1946, he noted a pulsatile swelling on the

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infrequently used for spontaneous aneurysms because of the difficulty of suturing vessel walls, the site of advanced degenerative disease. Excision, when not followed by complications, has given excellent results and has been

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artery just above the clavicle stopped the pulsations of the aneurysm and caused no apparent cerebral symptoms. Digital pressure could not be tolerated for more than 10 minutes because of pain.

Operation Performed May 3, 1948, with endotracheal cyclopropane anesthesia. Transverse incisions three inches long were made just above and below the aneurysm, and a vertical incision was made between the midpoints of the transverse incisions. Subplatysmal flaps were reflected. Hernia tapes were passed around the common carotid artery proximal and distal to the aneurysm, which was found to be fusiform in type (Fig

Fig 2

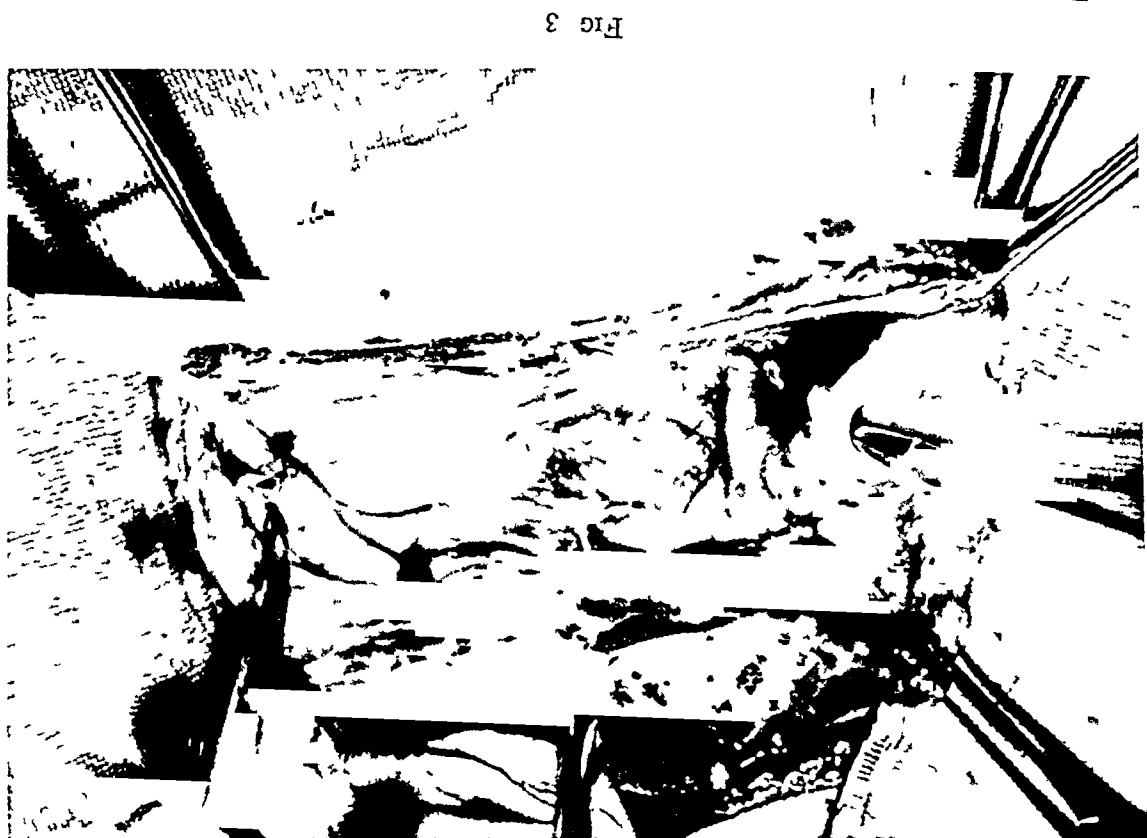
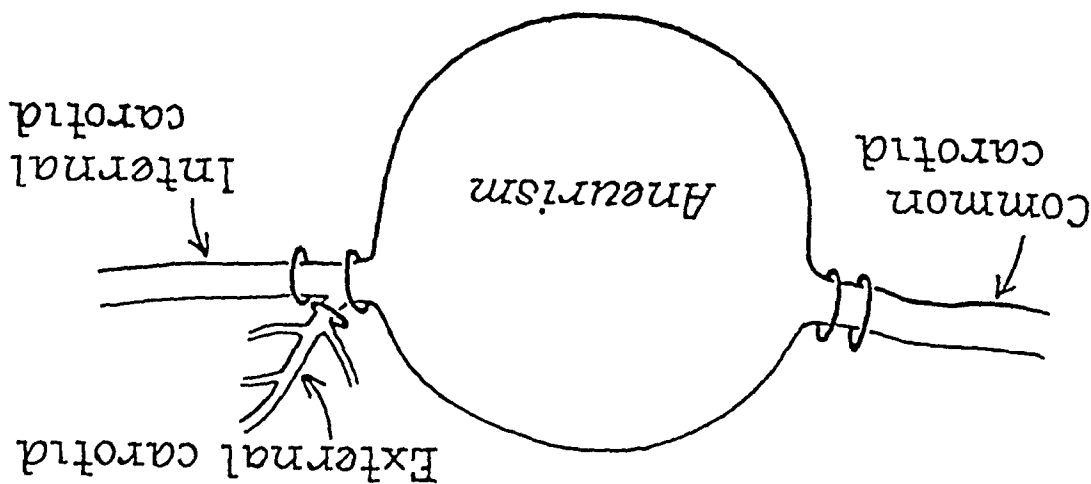


Fig 3

Fig 2—The configuration of the aneurysm and the points of ligation are shown diagrammatically.

Fig 3—A photograph taken at operation just after the sac was opened. Kelly clamps have been inserted into the common carotid artery proximal and distal to the aneurysm.

left side of the neck, just above the clavicle. Several months later a similar but smaller lump appeared on the right side of the neck. The lesion on the left increased gradually in size but that on the right did not. In January, 1948, the lump on the left, which was about the size of an orange, began to grow rapidly in size. Hoarseness, severe constant pain, and difficulty in swallowing developed. During the four months prior to admission he lost 40 pounds in weight.

Physical Examination. The patient was apparently in great pain, with a large pulsating mass on the left side of the neck (Fig 1). The trachea was displaced far to the right. Just above the right clavicle there was a pulsating tumor 2.5 cm in diameter. The left vocal cord was paralyzed. The blood pressure was 200/110 in both arms. The heart was moderately enlarged, and there was a soft, blowing diastolic murmur heard along the left border of the sternum. The peripheral arteries were sclerotic and tortuous.

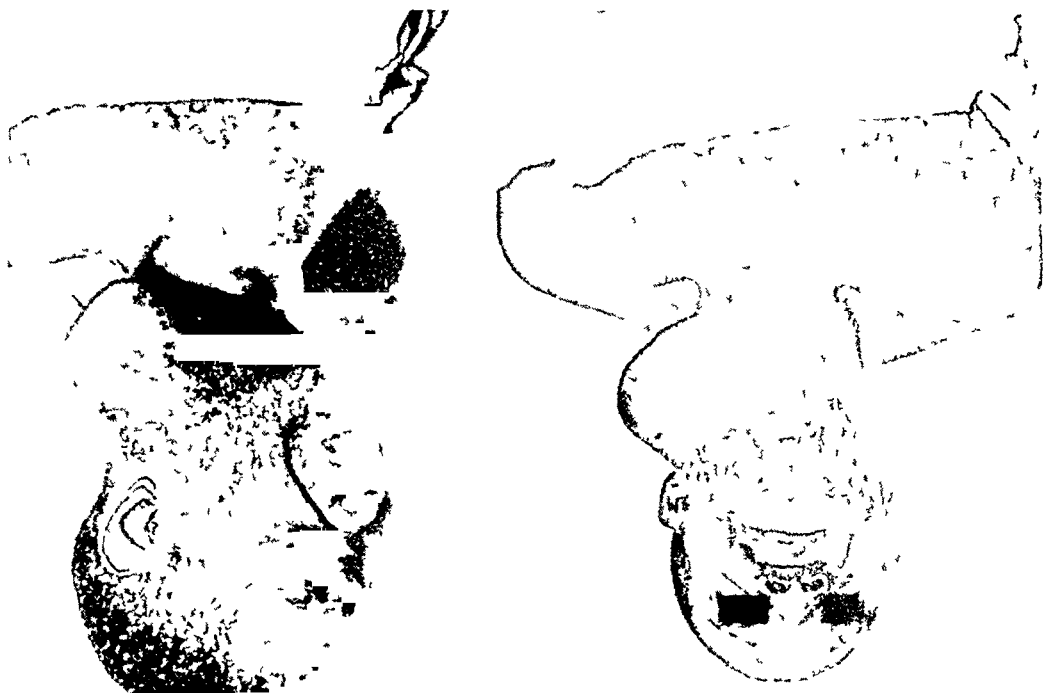


Fig 1—Photographs taken on admission, showing the size of the aneurysm of the left common carotid artery. The small aneurysm of the right common carotid artery is shown in (A).

A neurologic examination revealed no evidence of central nervous system syphilis. There were no other positive findings.

Laboratory Tests. A complete blood count, urinalysis, blood urea nitrogen, carbon dioxide combining power, serum protein and chloride were within normal limits. A blood Kolmer, Kline, and Wassermann were positive.

Chest Roentgenogram. There was moderate cardiac enlargement, particularly to the left, and moderate dilatation of the aortic arch.

Roentgenogram of the Tibia. There was thickening of the cortex and anterior bowing, consistent with a diagnosis of syphilitic osteitis.

Electrocardiogram. Normal except for left axis deviation.

Clinical Course. The patient was in constant pain and was unable to eat. Rupture of the aneurysm appeared imminent. A successful surgical attack on this lesion was obviously the only means of prolonging his life. Compression of the left common carotid

2) Adjacent structures, which were densely adherent to the wall of the aneurysm, were freed by sharp dissection. The left internal jugular vein and vagus nerve lost their identity in dense, matted scar tissue medial to the lesion. The dissection proceeded without difficulty except at a point on the lateral wall of the pharynx where the aneurysmal sac and pharynx were entered simultaneously. At this point only a thin layer of pharyngeal wall and aneurysmal sac remained as a barrier against rupture. The opening in the pharynx, about one-half inch in length, was closed with chromic catgut sutures. The aneurysm was then opened widely (Fig 3), and the dissection was completed. With noncrushing clamps applied to the artery proximally and distally, the sac was excised.

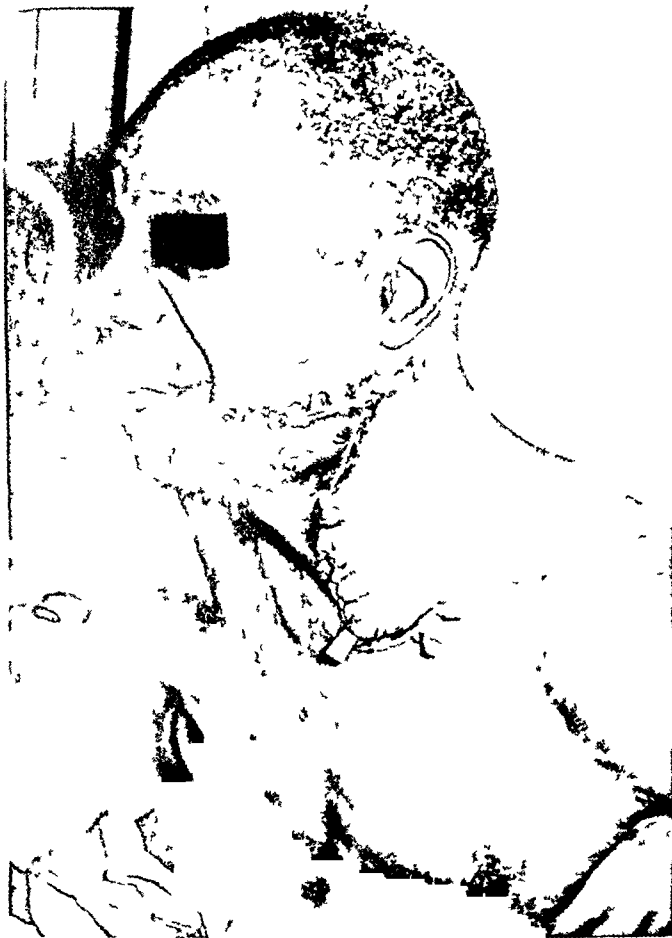


FIG 4—A photograph on the first postoperative day

Preparations had previously been made to use an arterial graft from a fresh cadaver. Because of advanced degenerative changes, the patient's carotid artery was tested with sutures. These were found to cut through easily. Because of this it was thought safer to avoid a graft if the collateral circulation could be shown to be adequate. This was tested in two ways. First, the clamp was removed from the distal end of the artery. The blood spurted, under strong pressure, for a distance of at least three feet. Second, anesthesia was stopped and the patient was permitted to wake up. It was found that the upper and lower extremity on the contralateral (right) side could be moved freely. With this evidence of adequate collateral circulation and the uncertainty of the suture-holding ability of the patient's vessel, ligation was considered preferable to a grafting procedure. Heavy silk ligatures were applied to the common carotid artery proximally.

and to the common internal and external carotid arteries distally. The wound was closed with one dependent drain, which was removed on the first postoperative day (Fig. 4). A tracheotomy was performed 36 hours after operation because of excessive tracheobronchial secretions with dyspnea and apparent respiratory obstruction. The patient was digitalized because of auricular fibrillation. There was no evidence at any time of cerebral ischemia or neurologic sequelae. The tracheotomy tube was removed after two weeks, and the patient was discharged on the 26th postoperative day. When last seen, eight months after operation, he had regained his normal weight and appeared well. The aneurysm of the right common carotid artery had become no larger.

COMMENT

In this elderly patient the use of three simple tests demonstrated that adequate collateral circulation had developed. Cerebral disturbances did not occur during carotid occlusion preoperatively, retrograde bleeding was in strong spurts when the distal clamp was removed during operation, and there was normal motor function on the contralateral side of the body following carotid occlusion during operation. It is not likely that such evidence of adequate collateral circulation will always signify freedom from cerebral complications in view of the late sequelae reported by Dandy¹⁶ and Schorstein¹⁷. The use of carotid intra-arterial pressure recordings during operation, suggested by Sweet and Bennett,²¹ may prove to be a useful refinement in evaluating collateral circulation. Although the equipment used by them was considered too complicated for routine use, a simpler and more compact instrument, such as that of Peterson, Dripps, and Risman,²³ in use in the operating rooms of the Hospital of the University of Pennsylvania, may be satisfactory.

Our experience with vein grafts in experimental animals and in patients,²⁴ and the experience of Gross²⁵ with artery grafts demonstrate that defects of large arteries can be satisfactorily bridged by grafting procedures. In elderly patients one is confronted with the problem of suturing a healthy graft to friable, arteriosclerotic vessels. The reliability of the suture method of anastomosis under such circumstances has not been established. The type of suture used may be a factor of importance. In an arteriosclerotic patient in whom Lexer²⁶ replaced a femoral artery aneurysm with a saphenous vein graft a Carrel suture cut through the friable arterial wall whereas a continuous everting mattress suture was entirely satisfactory. In patients with degenerative changes in the arterial walls the nonsuture method of Blakemore and Lord^{27, 28} may be useful.

SUMMARY

1. The problems of treatment of aneurysms of the common carotid artery and of ligation of the carotid arteries have been briefly discussed.

2. An instance of successful excision of an unusually large luetic aneurysm of the common carotid artery in an elderly patient has been described.

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POSTOPERATIVE DIABETES MELLITUS FOLLOWING RESECTION OF THE BODY AND TAIL OF THE PANCREAS FOR SECONDARY INVASION BY GASTRIC CANCER¹

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RECENT ADVANCES in the surgery of the pancreas have afforded interesting observations upon the physiology of this organ in man. For example, it has been found that the external pancreatic secretion is not essential to the maintenance of a normal nutritional status in some instances.¹ It has also been observed that the totally depancreatized human being presents only a relatively mild diabetes that is less severe than many instances of spontaneous diabetes in individuals with the entire pancreas in situ. More surprising is the fact that total pancreatectomy in the diabetic human has not resulted in augmentation of the severity of the diabetes already present.²

In previous experiences the head of the pancreas seemed to represent adequate tissue to permit normal carbohydrate metabolism, since in a number of instances where the body and tail of the organ were resected because of secondary invasion by neoplasm arising in an adjacent organ, postoperative diabetes did not develop. However, in the past several months three patients from the private service of one of us (A B) had the body and tail of the pancreas resected incident to total gastrectomy for gastric carcinoma and developed transitory postoperative diabetes for which insulin was administered. The case histories are summarized below.

Case 1—I B, a 57-year-old white housewife, first seen at Memorial Hospital on October 29, 1947, at which time she gave the following history. In June, 1938, the patient was submitted to a gastric resection, apparently for a small neoplasm of the stomach. Six months prior to the operation the patient developed epigastric discomfort associated with belching and slight weight loss. Subsequent to the operation the patient felt well, gained weight and had no complaints until the early fall of 1947, at which time the symptoms recurred—epigastric discomfort, weight loss and an increasing difficulty in swallowing solid foods. The patient was thoroughly studied and a diagnosis of recurring gastric carcinoma was made based upon roentgenographic appearance of the remaining stomach, the walls of this segment were quite rigid.

Physical examination at the time of admission to the Memorial Hospital showed a well-developed white female presenting signs of moderate weight loss but not in acute discomfort. Abdomen showed a well-healed midline scar and on palpation there was a definite epigastric fullness which was slightly tender. The liver was not enlarged, spleen and kidneys not palpated. Pelvic examination revealed no metastatic masses.

Preoperative laboratory studies (1) Blood chemistry: serum protein 5.5 Gm per 100 cc, blood urea nitrogen 15.0 mg per 100 cc, blood sugar analysis not done.

¹ Submitted for publication February, 1949.

(2) Blood Hemoglobin 78 per cent, white cells 83 (3) Urinalysis specific gravity 1022, reaction acid, color amber, *negative for albumen and sugar* (4) Chest film negative for metastases

Operation November 1, 1947 The findings were as follows The remainder of the stomach (the patient had had a previous gastrectomy) was involved in a large neoplastic process The previous gastro-intestinal anastomosis was obviously invaded by the tumor, the remaining gastro-hepatic ligament was short and grossly free of disease In the



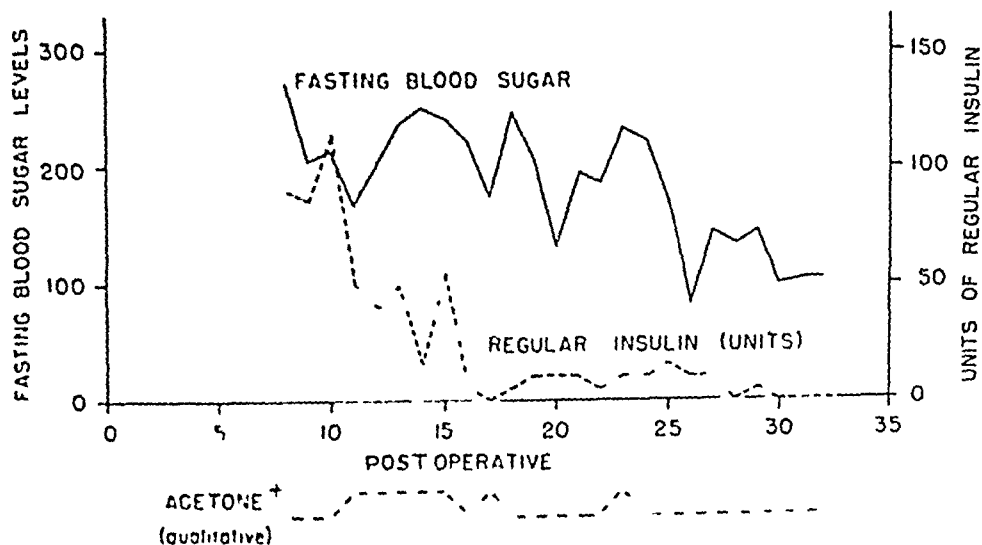
FIG 1—(Case 1) Photograph of posterior view of operative specimen consisting of residual upper third of stomach involved in recurrent carcinoma (a radical gastrectomy had been performed ten years previously for carcinoma) The spleen and entire body and tail of pancreas were resected also, as well as the loop of jejunum brought up for gastro-jejunostomy at the previous operation Mid-portion of transverse colon is not well shown in the photograph and was also removed

mesocolon two metastatic nodules were found The tumor was firmly adherent to the body of the pancreas The liver was free from metastases but contained a small mass located on the lower border of its right lobe which was bluish in color and grossly

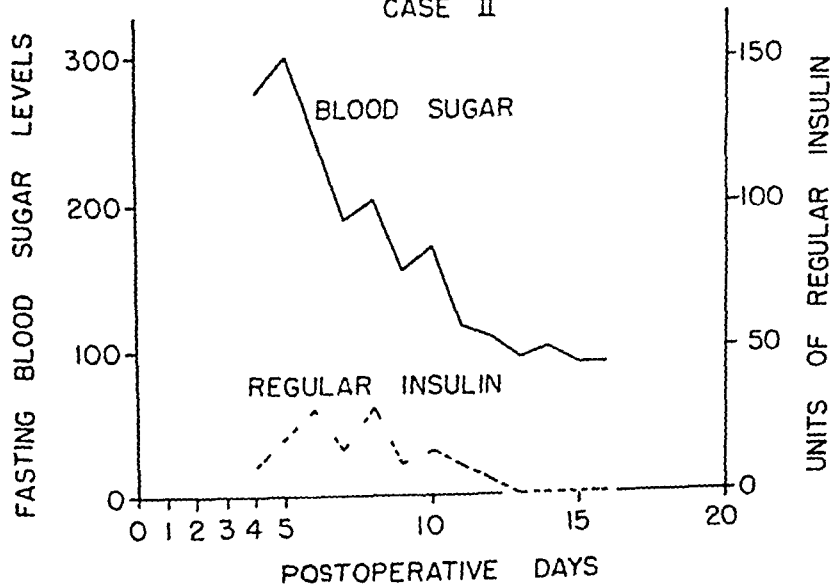
resembled a hemangioma. The remaining stomach, spleen, body and tail of pancreas and transverse colon were resected en masse. Resection of hemangioma of liver was performed. The alimentary tract was reconstituted by esophago-jejunostomy, entero-enterostomy, and colocolostomy (end-to-end). A photograph of the specimen is shown in Fig 1. The patient withstood the procedure satisfactorily and received 2,000 cc of blood and 1,000 cc of 5 per cent dextrose in distilled water during the operation.

FIG 2

CASE I



CASE II



ACETONE NEGATIVE THROUGHOUT POSTOP COURSE

FIG 3

Fig 2—(Case 1) Graph showing levels of morning fasting blood sugar observed after the eighth postoperative day. The postoperative diabetic state lasted until the twenty-sixth postoperative day after which it was very mild. Daily insulin intake is also shown.

Fig 3—(Case 2) Graph showing fasting morning blood sugar levels observed daily after the 4th postoperative day. The postoperative diabetic state lasted until about the thirteenth day. Daily doses of insulin also indicated.

Pathologic report "Signet-ring adenocarcinoma, Grade IV, with extension to gastrocolic ligament, peri-pancreatic fat, mesentery and nodes. The line of esophageal resection was involved along with the esophageal node, and there was cavernous hemangioma of the liver."

Postoperative course The immediate postoperative course was uneventful but by the ninth day physical signs and drainage from the upper part of the wound indicated the development of a subdiaphragmatic abscess. The upper angle of the wound was separated to increase drainage. Postoperative diabetes was not discovered until the eighth day when the urine showed 4+ reduction. Fasting blood sugar was 273 mg per 100 cc. Thereafter (see Fig 2), insulin was administered with or without infusions as the case may have been. During the 26 days following operation fasting blood sugars varied from 132 to 400 mg per 100 cc depending upon the activity of the subdiaphragmatic abscess. During the 4 last days in the hospital fasting blood sugars varied from 100 to 126 mg per 100 cc. She was discharged on the forty-second postoperative day with wound healed and no glycosuria.

During the winter of 1947-48, the patient was ambulatory and moderately active. By the end of March, 1948, there was recurrence of a palpable mass in the upper left quadrant of the abdomen and this gradually increased in size. There were periods of extreme thirst and a blood sugar determination showed 230 mg per 100 cc, on one occasion, with reduction in the urine of +++ to +++. Insulin in doses of 15 to 30 units a day was given. Recurrences of the neoplasm progressed until the patient died in June 1948, 8 months after the massive resection.

Case 2—W M, a 44-year-old salesman, was first seen at the Memorial Hospital on March 17, 1948, at which time the following history was obtained. In the early part of October, 1947, the patient first noticed occasional epigastric distress which had no relationship to the quality or amount of food ingested. This persisted and became associated with constipation and a feeling of general malaise. In November, 1947, the patient sought medical consultation for the first time and gastro-intestinal studies were suggestive of a gastric neoplasm. An exploratory laparotomy was advised but not accepted. The symptomatology gradually became more marked and in February, 1948, the patient finally submitted to laparotomy, performed in another institution, which revealed an extensive gastric carcinoma invading neighboring structures and, therefore, considered inoperable. The patient was made aware of the seriousness of his condition and he then sought further advice elsewhere.

Physical examination at the time of admission to the Memorial Hospital revealed a well-developed and well-preserved middle-aged male who was somewhat pale and showed evidence of some weight loss (20 pounds) but he was in no acute distress. In the abdomen there was a recently healed left upper paramedian scar and palpation revealed a large, firm, nodular mass somewhat fixed and poorly outlined in the epigastrium. The liver and spleen were not palpable. No other masses were palpated. There was no "rectal shelf" on digital examination.

Preoperative laboratory studies (1) Blood chemistry: Blood sugar 81 mg per 100 cc, blood urea nitrogen 12.5 mg per 100 cc, serum protein 6.9 Gm per 100 cc, serum chlorides 100 mg per 100 cc, serum bilirubin 1.0, hematocrit 46 per cent, prothrombin 75 per cent. (2) Blood: Hemoglobin 85 per cent, white cells 7.8 (with a normal differential). (3) Urinalysis: specific gravity 1.008, reaction acid, albumen and sugar negative. (4) Chest film: negative for metastases.

Operation March 20, 1948. The findings were as follows: Large, firm tumor apparently arising in the upper portion of the stomach and invading by direct extension the transverse colon and body of pancreas. Fairly large, firm nodes were found along the lesser and greater curvatures. The liver was free of disease and there were no peritoneal implants. The surgical procedure consisted of total gastrectomy, splenectomy, partial pancreatectomy (tail and body), transverse colectomy en masse, esophago-jejunostomy,

enteroenterostomy, colocolostomy (end-to-end) The patient withstood the procedure well, receiving 3,500 cc of blood and 1,000 cc of normal saline during the operation

Pathologic Report "Adenocarcinoma, Grade III, of stomach invading pancreas, wall and mucosa of colon, metastatic to nodes on greater and lesser curvature Negative spleen"

Postoperative Course The immediate postoperative course was satisfactory The blood pressure was maintained within normal limits and shock did not occur The patient did not receive anything by mouth for 9 days and was given 3,000 cc of parenteral fluids daily as follows Mornings 1,500 cc 5 per cent glucose in saline, afternoons, 1,500 cc 5 per cent glucose in distilled water On the fourth postoperative day at 2 00 A M the patient's blood pressure fell from 120/90 to 80/60, there was profuse perspiration The pulse was regular but somewhat weak and the remainder of the physical examination was negative Blood transfusion was given The urine was tested for sugar and was positive A fasting blood sugar determination was then obtained and found to be 277 mg per 100 cc 10 units of regular insulin were promptly administered Thereafter the use of small amounts of regular insulin was enough to control the diabetic state, (see Fig 3) Daily fasting blood sugar determinations were obtained thereafter On the third postoperative day the patient was out of bed and on the ninth postoperative day he was allowed to receive fluids by mouth He was discharged on the eighteenth postoperative day at which time there was no evidence of diabetes Six months after operation the patient remains clinically well and is free from diabetes

Case 3—W B, a 55-year-old white housewife who was first seen on April 15, 1948, at which time she gave the following history In January, 1948, the patient first noticed some weakness and general malaise which was associated with slight epigastric distress together with some difficulty in swallowing The patient saw her private physician who prescribed a diet and medication for symptomatic relief She felt somewhat improved, but within a few weeks the symptoms recurred A gastro-intestinal roentgenographic study was done and revealed the presence of a gastric neoplasm The patient lost approximately 6 to 8 pounds in weight and had been on a soft diet for the 2 months prior to her appearance Lately she had been complaining of a moderately severe pain in the back (pancreatic invasion?)

The past and familial histories were non-contributory Physical examination at the time of admission showed a well-developed and well-nourished white female who was not in acute distress There was some epigastric fullness and tenderness of the abdomen but no definite evidence of neoplasm was present, the liver was not enlarged and the spleen and kidneys were not palpable Rectal and pelvic examination revealed no evidence of metastases

Preoperative laboratory studies (1) Blood chemistry serum chlorides 106 mg per 100 cc, serum protein 6.0 Gm per 100 cc, blood sugar 71 mg per 100 cc, blood urea nitrogen 12.0 mg per 100 cc (2) Blood hemoglobin 95 per cent, white cells 6.4 (3) Urinalysis specific gravity 1.026, reaction acid, amber color and negative for sugar and albumen (4) Chest film negative for metastases

Operation April 27, 1948 A large fungating lesion was found apparently arising very high in the lesser curvature of the stomach, the tumor had invaded almost the entire stomach and was firmly adherent and fixed to the body of the pancreas, the liver was free from disease and there were no peritoneal implants The surgical procedure consisted of resection of the entire stomach and omentum, splenectomy, and partial pancreatectomy (tail and body) The operation was completed by esophagojejunostomy and enteroenterostomy The patient withstood the procedure well and received 1,500 cc of blood and 500 cc of saline during the operation

Pathologic report "Adenocarcinoma Grade IV of stomach, proximal and distal lines of resection are clear of tumor, diffuse lymphatic permeation of gastric wall by tumor with invasion of pancreas and metastases to omental nodes, negative spleen"

Postoperative course The immediate postoperative course was uneventful. The blood pressure was satisfactorily maintained within normal limits following the operation and shock did not occur. The patient received 3000 cc of parenteral fluids daily as follows: 1000 cc of amigen in the mornings and 2000 cc of 5 per cent glucose in distilled water (or saline) in the afternoons. On the first postoperative day fasting blood sugar determination revealed the presence of a hyperglycemia and thereafter an increasingly severe diabetic state persisted until death on the twelfth day (See Fig 4). The patient sat up on the second postoperative day and was out of bed on the fourth day. On the sixth postoperative day there was acetone in the urine for the first time. On the eighth postoperative day the patient had a sudden, sharp pain in the right lower chest which was associated with anxiety and shortness of breath; chest examination was entirely negative and the legs showed no evidence of phlebo-thrombosis. A tentative diagnosis of small pulmonary infarct was made. On the following day chest examination revealed a definite dullness in the right lower lobe posteriorly, a chest film was reported as not indicative of pulmonary infarct. On the tenth postoperative day there was a definite swelling of

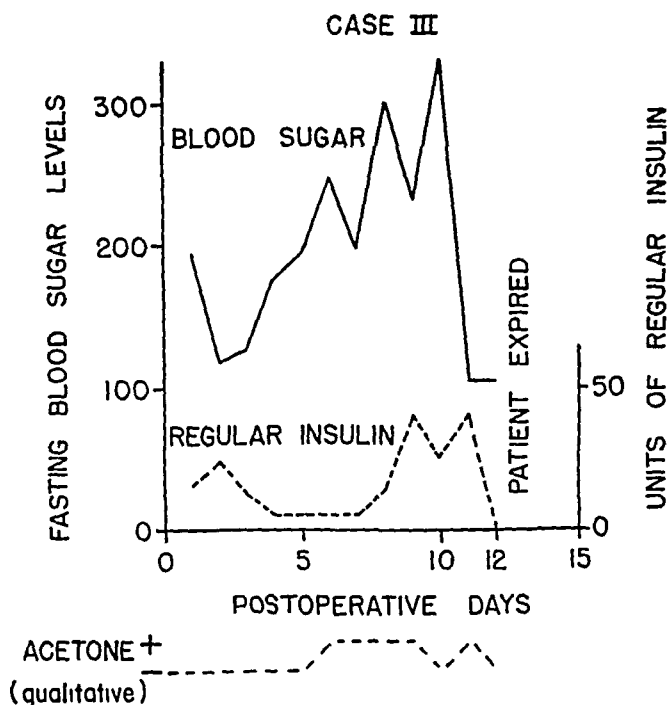


FIG 4—(Case 3) Graph of morning fasting blood sugars showing postoperative diabetic state. Patient died on the twelfth day.

the left leg. On the twelfth postoperative day the patient's condition deteriorated rather rapidly and she expired. Necropsy was not obtained. The rather sharp increase in the diabetic state after the fifth postoperative day is indicative of some disturbance probably associated with the fatal outcome but the exact nature of which was not determined in the absence of necropsy.

DISCUSSION

Post partial pancreatectomy diabetes in man where the pancreas was presumably normal does not appear to have been previously cited in the literature. However, in the case where the pancreas presented inflammatory disease it has been noted. Mallet-Guy, Chambon and Plauchu³ describe a patient in whom there was mild preoperative diabetes (glycemia, 160 mg per 100 cc) and

following resection of 40 Gm of the body and tail, which portions were enlarged and tumefied (histologic study showed chronic fibrous pancreatitis), the fasting blood sugar reached levels of 176, 208 and 301 mg per 100 cc on three days respectively. Insulin was administered in daily doses up to 60 units and by the end of 15 days fasting blood sugars were again at normal levels. Mallet-Guy interprets these findings as indicating that the presence of a large inflammatory process in the pancreas interferes with its normal function, hence the preoperative diabetes, and that resection of the affected areas permitted a return to normal function of the remaining unaffected portions of the gland, hence the eventual disappearance of the diabetes.

In the case cited by Leiche¹ the patient was diabetic before subtotal pancreatectomy was performed for severe pain due to marked chronic pancreatitis with pancreato-lithiasis. In the weeks following the operation the diabetes seemed to increase in severity. This is explained by the disease, already present in the remaining portion of pancreas, which might have continued to progress.

In the three patients herein reported the pancreas was presumably normal in each instance. Following resection of the body and tail, the remaining head of the organ appeared unprepared to function normally for carbohydrate metabolism. This led to the use of insulin. In Case 1, the diabetic state lasted for practically three weeks after its discovery on the eighth postoperative day. In Case 2, no insulin was required after the thirteenth day. The third patient succumbed before opportunity was afforded to observe the duration of the surgically induced diabetes but the latter was severe due to disturbances of unknown type and, as stated, undoubtedly associated with the fatality.

The recurrence of diabetes in Case 1, a few months after its apparent subsidence, suggests further destruction of the remaining pancreas by recurrent neoplasm. Another explanation is that the patient might have been in the process of developing diabetes and that the resection of most of the pancreas hastened the evolution of this condition. It is interesting to speculate upon the question of whether or not these patients who did develop the transitory postoperative diabetes were in the process of developing the disease but had not yet manifested it clinically. This appears to be a logical hypothesis to explain why a few patients do and most patients do not develop transitory diabetes following resection of the body and tail of the pancreas.

SUMMARY

Case histories are presented showing the development of diabetes following resection of the body and tail of the pancreas for secondary invasion by gastric cancer. The pancreatic tissue itself in these patients appeared normal on histologic examination.

Postoperative diabetes is to be anticipated in some instances where the body and tail of a presumably normal pancreas are excised. The immediate prognosis of such a diabetic state appears to be good since the induced diabetes seems to be transient.

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THE CLINICAL USE OF POLYETHYLENE TUBING FOR INTRAVENOUS THERAPY¹

A REPORT ON SEVENTY-TWO CASES

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INTRODUCTION

INTRAVENOUS THERAPY may present serious difficulties in the management of the severely ill patient. The number of veins available for parenteral treatment often diminishes alarmingly through sclerosis, from trauma and overuse. Patient welfare and the efficiency of the house staff are severely affected.

Indwelling needles have been tried in the past, but they have obvious deficiencies.¹ The sharp point and inflexibility unduly traumatize the vein and make it difficult to maintain the needle in the vein without seriously limiting the patient's movements. Clotting of the needle and phlebitis of the injected vein are common complications. The need for a practicable method of venous intubation has increased with frequent use of large infusions in surgical and medical practice. At the suggestion of Dr. H. W. Smith of New York University, the use of plastic tubing for intravenous infusions was investigated.

The purpose of this paper is to demonstrate that these difficulties may be overcome by intravenous catheterization with plastic tubing. The tubing used was polyethylene (polythene)[†] in postoperative patients on the surgical service at Memorial Hospital. There have been scattered references to intravenous plastic tubing in the literature,^{2,5} but thus far these have represented small series of patients in whom the cannula was in place for a relatively short period of time.

Zimmerman² discussed the use of a vinylite tube in 11 dogs for periods of from four to five weeks without untoward effects. Venous thromboses were found in two dogs and were thought to be due either to the sclerosing properties of the injected solutions or to the mere presence of the plastic.

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† The tubing and equipment were obtained from Becton Dickinson Company, Rutherford, N. J., through the courtesy of Mr. Oscar Schwidetsky.

‡ The cooperation of the surgical staff of Memorial Hospital is gratefully acknowledged.

catheter in the vein MacQuigg⁶ reported a series of observations using a polyvinyl chloride tubing for intramuscular injections in humans

Meyers³ was the first to report the clinical use of polyethylene* tubing. He used polyethylene tubing in administering heparin and plasma to two patients for a period of several days. Guenther, *et al*,⁴ used polyethylene tubing for intravenous therapy in 18 cases for periods up to two weeks. They noted "the most satisfactory results were obtained in continuous infusion of solutions of penicillin and heparin." Diamond and Thomas⁵ have used polyethylene tubing of large caliber in the treatment of newborn babies with erythroblastosis. The tubing was inserted through the umbilical vein into the vena cava and left in place for three hours. Five hundred cubic centimeters of the infant's blood was replaced with Rh negative blood, and no reaction of the veins was noted.

There have been two extensive experimental studies^{7, 8} with polyethylene in neuro-surgery in which the plastic was shown to fulfill the requirements of a dural substitute. Segments of polyethylene tubing implanted into the brain for as long as 90 days caused no significant inflammation. In contrast, another plastic, cellophane, when implanted into brain tissue caused an early and marked inflammation with leucocytosis and gliosis.

Poppe and De Oliveira⁹ investigated methods of obliterating aneurysms by inducing fibrosis around them with irritating plastic films. They used a material "polythene cellophane" in four human cases and produced marked fibrous reactions around the aorta. This was attributed to the use of an impure plastic. Yaeger and Cowley¹⁰ have recently used polyethylene as a fibrous tissue stimulant in the treatment of aneurysms and recurrent hernias. Pure polyethylene had no tissue reaction whereas polyethylene with dicetyl phosphate retained from its preparation produced a marked reaction.

Hurwitt¹¹ recently reported the use of polyethylene tubing in animals as a vascular shunt to overcome pulmonary stenosis. Hackworth¹² replaced the thoracic aorta with polyethylene in dogs. In both studies clotting in the tube, and tissue reaction, were reported minimal.

Ferris and Grindlay¹³ have adapted polyethylene to various urologic procedures. Both polyvinyl chloride and polyethylene had distinctly less encrusting from urinary salts and organic material than the usual rubber catheter.

Brown¹⁴ and his co-workers have attempted direct methods of anastomosing the common bile duct, trachea, and pelvic colon respectively with molded polyethylene tubes. In these studies they noted no tissue reaction to polyethylene and no tendency for the plastic to deteriorate or for the tubes to become blocked with secretions or solid material.

DESCRIPTION OF POLYETHYLENE

Industry has developed a large variety of plastics but very few have been found to be sufficiently well tolerated in tissue to be of value in surgical

* "Med-o-seal," A C Balfour Co, Englewood, N J

work. Studies with polyethylene have produced such varying results that it is of vital necessity that those using it be absolutely familiar with the physical and clinical properties of the product.

Polyethylene (polythene, Med-o-seal) is a thermo-plastic, synthetic resin and has probably the simplest formula of all the plastics. It consists of carbon atoms joined into chains, each carbon carrying two atoms of hydrogen. These chains consist of several hundred to more than a thousand such units with a molecular weight of approximately 18,000.

Polyethylene is produced commonly by two methods. The first is by "solvent cast" with the use of stippling agents, plasticizers and antioxidants. This frequently results in an impure plastic as noted by Yaeger and Cowley.¹⁰ The preferable method of preparation is by "extrusion," wherein the plastic is converted by heat and pressure into the desired tubing.

The latter product, which we found best adapted to our uses, is flexible, chemically inert, fluid repellent, and inexpensive. It is not affected by concentrated hydrochloric, sulfuric, and hydrofluoric acids, and it resists concentrated sodium hydroxide. The plastic is resistant to tissue fluids at body temperature for prolonged periods. It has the non-coagulant property that characterizes paraffinic products when they are brought into contact with blood.

METHOD OF STUDY

A Choice of patients. The patients in this series ranged in age from 18 months to 74 years. They were, in general, studied following major surgery, when intravenous therapy was extremely difficult and in a few instances almost impossible. The technic was employed solely by the Department of Clinical Investigation at the request of the surgical services. A close record was kept indicating length of time that the tubing was left inserted, type of solution given through the tube and any complications which ensued.

B Technic. Two different calibers of tubing were available. The smaller caliber (for penicillin and heparin therapy) passed through a thin wall BD No. 17 needle. The larger, which was used when blood, plasma, or protein solutions were to be administered, or when rapid infusion might be needed, was inserted via a No. 14 BD needle. The intravenous tubing and accessories set are kept as a unit on a small cart which can be readily transported to the bedside (Fig. 1). It has been our practice to boil the tubing in glass tubes which prevent bending of the plastic. They are then stored in a tray containing 1 to 1000 aqueous solution of benzalkonium chloride (Zephiran Chloride NNR). Polyethylene does not withstand autoclaving, due to its low melting point.

The appropriate vein is selected and the field prepared and draped with the usual sterile precautions. A small amount of 1 per cent novocaine is given intradermally and subcutaneously, and a small incision is made with a No. 5 Bard Parker blade.

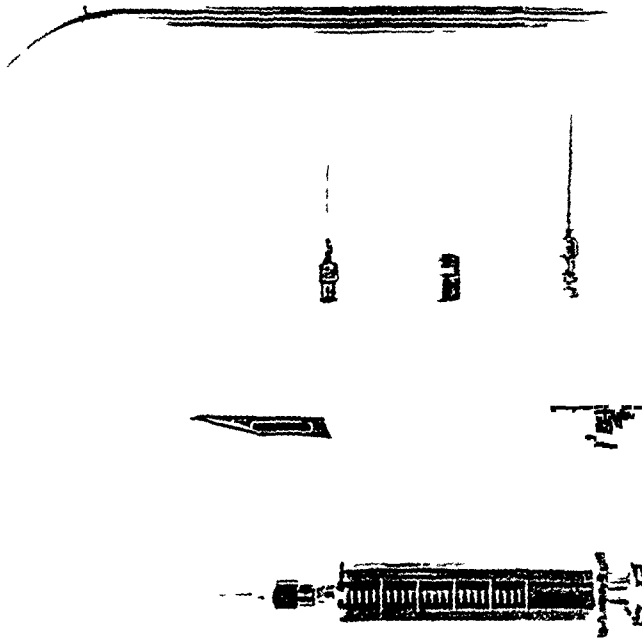


FIG 1—Unit of intravenous tubing and accessories



FIG 2



FIG 3

FIG 2—Insertion of tubing after the syringe is detached, and with the needle held carefully in place, the plastic tubing is passed into the vein
FIG 3—Jugular tubing maintained in place with a butterfly adhesive and suture tied around it

The thin wall No. 14 BD needle is inserted into the vein using a 5 cc syringe loaded with 1 cc of heparin—a small amount of which is injected into the needle as soon as it enters the vein. The syringe is then detached and, with the needle held carefully in place, the plastic tubing is passed into the vein for a varying length, depending on the site selected (Fig. 2). A small amount of heparin is instilled into the plastic tube prior to insertion. With digital pressure over the vein holding the tubing in place, the needle is withdrawn. A blunt nosed No. 18 BD needle is inserted into the free end of the tubing and the remaining heparin injected into the tube to prevent clotting.

If an infusion is to be started it may be attached by using a Luer-Lok adaptor. Otherwise the tube may be effectively sealed off with a Luer-Lok plug. Jugular tubing is best maintained in place with a butterfly adhesive and suture tied around it (Fig. 3). Elastic adhesive adds stability and is sufficient when the femoral vein is used.

The tubing is rinsed out with sterile isotonic saline following plasma or blood infusions. Following each use or at least twice a day, $\frac{1}{2}$ to 1 cc of heparin* should be instilled into the tube. This may be discontinued after the first four to five days if the tube is being maintained with constant infusions of isotonic aqueous solutions.

Changes of the direction and position of the tube are sometimes necessary to permit freer movement of the patient and more ease in infusing and withdrawing specimens through the tube. The withdrawal of blood specimens is facilitated by the use of a tube with several lateral openings at its distal end. Continuous intramuscular therapy may be carried out by the insertion of the smaller catheter through a long No. 17 BD thin wall needle under the fascia lata of the thigh.

C Choice of vein The arm, while frequently presenting large veins, has obvious limitations. The catheter must be inserted proximal to the ante cubital fossa to avoid valves and bending at the elbow. Arm motion also causes mechanical irritation of the vein by the tubing unless it is inserted for a sufficient distance to enter a large vessel. It has been our experience that when the tubing occludes the vein, edema results, probably as a result of mechanical irritation. In this study the large veins, *i.e.*, jugular and femoral, were found to be the most satisfactory location for intravenous catheterization.

RESULTS

The tubing first utilized in this study was polyvinyl chloride similar to the one used by McQuigg for intramuscular injections. In our preliminary series of eight patients several local reactions† occurred which led to the use of polyethylene on the theory that it represented a purer plastic.¹⁵

* Five to 10 mg Heparin Sodium, Upjohn

† We believe these reactions were due to impurities in the preparation of this tubing since we are now using a BD polyvinyl tubing with excellent results.

The observations made in this study are summarized in Figures 4 and 5. Successful intubation was achieved in 54 cases out of a total of 72. The results were completely satisfactory in 42 cases out of 48 where large veins (jugular and femoral) were catheterized. In no cases was it impossible to introduce the

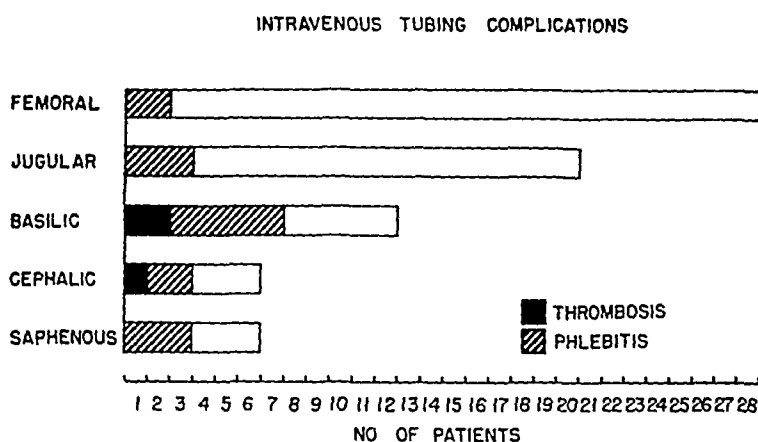


FIG 4

tube, although repeated attempts were necessary in some instances. One jugular tube remained patent for 39 days and was removed electively without complication.* A femoral tube was similarly effective for 35 days.

Symptoms of mild phlebitis were noted in 16 cases. These consisted of a temperature elevation, and pain, or edema in the area intubated. Frank throm-

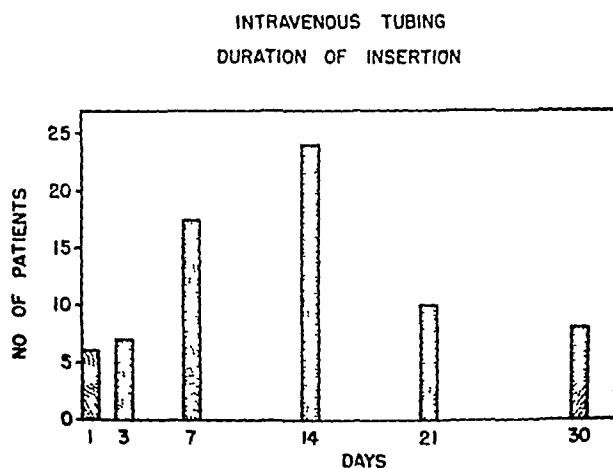


FIG 5

bosis was encountered in three cases where smaller veins were used. It is interesting that these thromboses occurred at three, eight and 17 days respectively. We have tended to be conservative and remove the tubing at any evidence of local reaction.

* A short clinical history of the patient is appended to this report.

DISCUSSION

Intravenous catheterization has proved its value in this series of 72 patients. The indwelling tubes alleviated patient discomfort and were convenient and time saving to the house staff. The tubing was well tolerated and provided considerable patient mobility. Blood, plasma, and hypertonic solutions were given without difficulty and at a satisfactory rate.

From the data reported above, it appears that the biggest disadvantage of indwelling intravenous catheters is local irritation to the vein. This irritation is probably mechanical in nature since it tended to occur where small veins were used. This drawback was circumvented by intubating the jugular (cervical) or femoral veins. Close observation during the initial period to insure proper placement and function of the tube is desirable. Thus, the possible complication of too rapid infusion is obviated. The theoretical possibility of aspiration of air is prevented by having the patient in a recumbent position with the open end of the tubing below the heart when specimens are withdrawn or infusion started. Careful technic with the femoral puncture is indicated to prevent possible reflex arterial spasm. In patients who have undergone extensive lower abdominal surgery we do not use the femoral route due to the possibility of further complicating an established phlebitis.

Further modifications of technic, particularly the use of a smaller tubing for peripheral veins, are indicated. Such a plastic tubing inserted in the operating room under anesthesia at the beginning of the operation would add to the patient's comfort and facilitate parenteral therapy during the early postoperative period.

SUMMARY

Therapy was carried out by means of indwelling intravenous polyethylene tubing in a series of 72 cases.

Ten local reactions, including three frank thromboses, were encountered in 18 patients whose arm veins were used. Six minor reactions occurred in 43 patients in whom the jugular or femoral veins were employed.

In one case the tubing was maintained for 39 days.

The procedure of intubation is presented and its limitations and advantages are discussed.

CASE HISTORY

M. P., Hospital No. 75596, a 26-year-old female with Hodgkins disease was admitted to the Research Ward for study of a progressive anemia following radiation and HN_2 therapy.

It was felt that the possibility of hypersplenism suggested by the anemia and the splenomegaly justified splenectomy, which was carried out on January 17, 1948. The operation was complicated by a severe hemorrhage, necessitating intra-arterial transfusion.

Venipuncture was extremely difficult in the immediate postoperative period due to shock, multiple vein ligations and sclerosis from previous chemotherapy. A polyethylene tube was inserted into her left jugular vein on the first postoperative day.

For several weeks parenteral feeding and hydration were carried out through this tube. As much as 3500 cc of fluids were administered in 24 hours without any difficulty or discomfort. Infusions were stopped nightly without plugging of the tube.

After 39 days the tube was removed, and the patient was discharged. The jugular vein was not palpably thickened. The small sinus tract which remained, healed completely in 24 hours.

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THE EFFECT OF DIATHERMY UPON ABDOMINAL ADHESIONS*

AN EXPERIMENTAL STUDY

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USE OF DIATHERMY IN PROPHYLAXIS OF ABDOMINAL ADHESIONS

Historical background Smith¹ in 1940 reported the use of fever therapy in two cases of mechanical small bowel obstruction due to pelvic inflammatory disease. These cases had both been characterized by repeated episodes of bowel obstruction due to intraperitoneal adhesions resulting from old gonococcal pelvic infection. Following fever therapy treatments using the Kettering hypertherm for two to three hours at intervals of one to three days for four to six treatments further episodes of intestinal obstruction did not occur. The value of hyperthermia in cases of gonococcal and non-specific pelvic inflammatory disease had been previously noted by other workers in this field.

During the period of 1942-3 ten cases of bowel obstruction due to intraperitoneal adhesions were treated at the University of Minnesota Hospitals with short wave diathermy following enterolysis. The following case is cited as an example.

Case History—In 1919 this 42-year-old male (U. H. No. 725832) had an appendectomy for a perforated appendix. Subsequent to this operation two laparotomies had been performed for adhesive bowel obstruction. In 1942 a total colectomy was performed at the University of Minnesota Hospitals, numerous adhesive bands were divided at the time of this operation. Two weeks later the patient developed a mechanical small bowel obstruction due to adhesive bands. Laparotomy and enterolysis were performed. During the first seven postoperative days the patient received short wave diathermy treatments. Three 15-minute treatments were given daily, employing the coil with 135-140 M. A. dosages. The subsequent course was uneventful and no further attacks of bowel obstruction ensued.

No specific therapeutic effect of short wave has ever been shown other than that due to the heat production within the tissues. Carlson and Orr² studied the effect of heat applied to the abdomen of dogs. Moist flannel covered by an electric pad at a temperature of 106-109° F. was used for one hour and the temperature in the midcolon checked by means of a long rectal thermometer. An average rise of temperature within the colon of 12° F. and an average body temperature rise of 5° F. was noted. Kymographic tracings of the dog's jejunum made during the application of heat showed no change in intestinal tone or movements. They also found that the prolonged (three hours) application of heat did not cause any significant increase in the intra-abdominal temperature. Tuttle and Fitts³ studied the effect of short

* Supported by a Research Fund from the Graduate School of the University of Minnesota. Submitted for publication March, 1949.

wave diathermy on various phases of skeletal muscle activity and found all phases to be shortened with the greatest change occurring in the period of relaxation Schlaepfer⁴ noted a slightly increased rate of intestinal contraction after diathermy, but no increased strength of the contractions. He found little roentgen-ray evidence of increased intestinal activity with diathermy.

On the basis that short wave diathermy appeared to have had a favorable effect on redevelopment of intraperitoneal adhesive bowel obstruction in the patients so treated at the University of Minnesota Hospitals, an experimental study was carried out on dogs to determine the effect of diathermy on intra-abdominal adhesions.

Methods of producing adhesions Two technics were employed to produce the adhesions.

1 In one series of dogs adhesions were produced by rubbing the terminal two feet of small bowel with dry gauze followed by the application of 7 per cent tincture of iodine to the traumatized bowel. Laparotomy was repeated two to four weeks later and the extent of adhesive formation was estimated. The usual finding was a coiling up of the terminal two feet of small bowel with dense adhesions between the coiled loops and adhesive bands between the traumatized bowel and parietal peritoneum and omentum. The adhesions were divided by sharp dissection with careful attention to hemostasis.

2 Ordinary glove talcum powder was used to produce adhesions. Under intravenous nembutal anesthesia the terminal two feet of small bowel was very gently scarified with dry gauze and a minute amount of autoclaved talc powder (always less than 5 Gm) was dusted over this bowel surface and the abdomen closed. Laparotomy was repeated one to three weeks later and in every instance dense adhesive formation had resulted. The traumatized bowel was usually coiled up in a dense adherent mass with the omentum adherent thereto. Small granulomatous areas were usually present on the mesentery, omentum, and serosal surface of the small bowel.

General effects of diathermy Observations were made on the effects of short wave diathermy on the exposed bowel, intra-abdominal and rectal temperatures and respiratory rate of the anesthetized dog and on the rectal temperature and respiratory rate of the non-anesthetized dog. Increased respiratory rate is the outstanding effect of short wave diathermy on the dog. Respirations become rapid and panting within a few minutes after the application of the diathermy coil or pads.

The average respiratory rate of a dog at rest is 15 to 25 a minute. Diathermy rapidly increased the rate to 100 to 300 per minute. Hemingway⁵ has shown that this increased rate is associated with a decreased tidal volume, supporting the theory that the heat stimulation causes a rapid air movement over the moist surfaces of the mouth, tongue, and pharynx without too great an air movement in the lung alveoli.

Effects of diathermy on the anesthetized dog The dogs were anesthetized with intravenous nembutal, the diathermy pads applied to the sides of the abdomen, the abdomen opened through a midline incision, and observations

made on the local effects on the exposed bowel, intra-abdominal and rectal temperatures, and respiratory rate. Within a few minutes after institution of the diathermy treatment, the bowel became edematous and hyperemic and small droplets of fluid appeared on the serosal surface. Increased peristaltic activity, manifested by increased rate and strength of intestinal contractions, was noted.

TABLE I—*Effects of Diathermy on Anesthetized Dog*

Dog No	Dosage (M A)	Length of Treatment	Total Temperature Rise		Respiratory Rate Per Minute		Rectal Temperature Rise During First 15 Min of Diathermy	Respiratory Rate Increase During First 15 Min of Diathermy
			Rectal	Intra abd	Initial	Final		
1 No 9	3 000	70 min	3.3°C	3.7°C	20	260	1.7°C	24
2 No 5	1 500	27 min	7 °	8 °	20	300	1.5°	16
3 No 6	3 000	115 min	1.1°		16	208	1.4°	70
4 No 29	3 000	45 min	3.9°	4.6°	12	86	1.4°	2

Table I summarizes the effects of diathermy on the anesthetized dog. Dogs No 4, 5, 6 and 29 expired after a precipitous rise in temperature. Autopsy revealed a grayish cooked appearance to the small and large bowel, with congestion, edema, and petechial hemorrhages scattered over the serosa and mesentery. The abdomen was not reopened in dog No 6.

Table II summarizes the effects of diathermy on the non-anesthetized dog. With identical dosages of diathermy the maximum rectal temperature

TABLE II—*Effects of Diathermy on Non-Anesthetized Dog*

Dog No	Dosage (M A)	Length of Treatment	Total Temperature Rise		Respiratory Rate Increase		Rectal Temperature Rise During First 15 Min of Diathermy	Respiratory Rate Increase During First 15 Min of Diathermy
			(Rectal)		Initial	Final		
1 No 8	3 000	30 min	6°C		26	180	4°C	155
2 No 9	3,100	110 min	2°		80	320	0	180
3 No 10	3,000	65 min	1.6°		40	280	1.6°	170
4 No 11	4,500	40 min	3°		100	260	3°	140

rise was 7° C in the anesthetized dog as compared to 1.6° in the non-anesthetized dog. There was a lag in the increased rate of respiration in the anesthetized dog receiving diathermy, two of the four dogs showing little change until shortly before death. The best guide as to diathermy effect in the non-anesthetized dog was the respiratory rate. There was no safe guide as to what constituted a safe dosage of diathermy in the anesthetized dog.

EXPERIMENTAL STUDY ON USE OF SHORT WAVE DIATHERMY IN RELATIONSHIP TO FORMATION OF INTRA-ABDOMINAL ADHESIONS

In the experimental study to be described the diathermy treatments were not begun until the first postoperative day. The treatments were given for prolonged periods (one to six hours) and the dosage guided by the tolerance

of the dog When the dog showed evidence of fatigue and excessive panting respiration the heat was discontinued for a few minutes In one dog diathermy treatment was instituted immediately after completion of enterolysis and while the dog was still under the influence of the anesthetic After one hour the temperature showed a precipitous rise, respirations became shallow and irreg-

TABLE III—*Diathermy Treated Dogs*

Dog No	Method of Producing Adhesions	Average Dosage	Duration of RX Daily (Average)	Temp Rise (C) (Average)	Resp Rate Rise (Average)	No of Days Dia-thermy RX Given	Degree of Reformation of Adhesions After Diathermy RX	Bowel Obst
1 No 49	Tr iodine	3800 M A	60 min	6°	20-200	10	More extensive	No
2 No 52	Tr iodine	3600 M A	80 min	4	16-210	14	Slightly less	No
3 No 53	Tr iodine	3500 M A	75 min	5	20-230	9	More extensive	No
4 No 38	Tr iodine	4000 M A	60 min	1 1	18-190	7	More extensive	No
5 No 13	Talcum powder	3500 M A	180 min	4	28-240	4	More extensive	No
6 No 16	Talcum powder	3200 M A	250 min	5	34-260	6	More extensive	No
7 No 17	Talcum powder	3400 M A	200 min	3	48-215	7	More extensive	No
8 No 25	Talcum powder	3600 M A	180 min	2	20-200	9	More extensive	No
9 No 18	Talcum powder	3500 M A	160 min	3	26-216	8	More extensive	No
10 No 27	Talcum powder	3500 M A	180 min	3	24-200	9	More extensive	No
11 No 10	Talcum powder	Dog expired while receiving diathermy immediately post op and while yet under anesthesia						

ular, and death quickly ensued The reason for the intolerance to diathermy under general anesthesia is not clear, but the danger was sufficiently definite to contraindicate its continued use in the anesthetized animal

Two series of experiments were run, one employing tincture of iodine and the other talcum powder to produce the adhesions A total of 22 dogs was

TABLE IV—*Controls*

Dog No	Method of Producing Adhesions	Degree of Reformation of Divided Adhesions	Bowel Obstruction
1 No 47	Tr of iodine	Greater	No
2 No 54	Tr of iodine	Greater	No
3 No 55	Tr of iodine	Greater	No
4 No 44	Tr of iodine	Greater	No
5 No 56	Tr of iodine	Greater	No
6 No 2	Talcum powder	Greater	No
7 No 14	Talcum powder	Greater	No
8 No 19	Talcum powder	Same	No
9 No 1	Talcum powder	Greater	Yes
10 No 8	Talcum powder	Greater	Yes
11 No 12	Talcum powder	Greater	Yes

studied, 11 of which served as a control group Laparotomy was performed three to four weeks after the production of the adhesions and a quantitative estimate made of the extent of the adhesive process Diathermy treatments were begun the following day and given daily thereafter for four to 14 days Laparotomy was repeated one to two weeks following the last diathermy treatment and again a quantitative estimate made of the extent of adhesive

formation. Tables III and IV summarize the data in the diathermy treated and the control series of dogs.

Summary. The clinical impression that short wave diathermy is of value in prevention of formation of intra-abdominal adhesions was not substantiated by experimental evidence. Although no obstruction occurred in the treated group of dogs, the extent of reformation of divided peritoneal adhesions was the same in the diathermy-treated dogs as in the control series.

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THE EFFECT OF DICUMAROL UPON POSTOPERATIVE PERITONEAL ADHESIONS*

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Reports by Lehman and Boys^{1,2} and Miki and Santani⁶ have suggested that the incidence and extent of postoperative peritoneal adhesions may be reduced by the introduction of heparin into the peritoneal cavity at the time of operation and in the early postoperative period. Subsequent work⁷ seems to cast doubt on the effectiveness of this means of therapy. Since this problem is in a state of flux and since no adequate means of therapy is available at the present, this study was undertaken to determine the effect of Dicumarol[‡] on peritoneal adhesions. Dicumarol, like heparin, is a potent anticoagulant, although its mode of action is different.^{8,11} However, the end result in regard to fibrin formation is the same.^{12,14} The method by which healing and hence adhesion formation occurs is well known and will not be reviewed here. Suffice it to say that fibrin must be present before the formation of scar tissue can take place. The rationale behind the use of anticoagulants to diminish the development of peritoneal adhesions depends upon their ability to effect a reduction in the amount of fibrin which can be formed.

Adequate animal experimentation and clinical use have already shown that surgical procedures can be safely carried out in the presence of a lowered prothrombin activity produced by Dicumarol, provided complete hemostasis is obtained before the incision is closed.⁸

METHODS

Twenty-six healthy mongrel dogs, weighing from 4.8 to 11.5 Kg were used in these experiments. They were divided into three groups: (1) a control group of six animals, (2) an experimental group of 14 animals, and (3) a severely dicumarolized group of six animals.

In groups one and two, preliminary operation consisted of laparotomy and abrasion of the serosal surface of the small bowel with dry gauze. Four segments of bowel 15 cm long and equally spaced between the ligament of Trietz and the ileocecal valve were rubbed lightly with a pad of dry surgical gauze. Slight oozing of the rubbed area was produced intentionally in all cases. This bleeding ceased spontaneously before closure. The surface area of the serosa damaged by this procedure was approximately 150 square cm. At the close of the operation 2.5 Gm of crystalline sulfanilamide was sprinkled in the peritoneal cavity to aid and abet the formation of adhesions.¹⁵

All animals were anesthetized with intravenous Nembutal (initial dose 30 mg per Kg, additional amounts as necessary). Hemostasis in all opera-

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‡ Dicumarol is the registered collective trademark of the Wisconsin Alumni Research Foundation, which controls the use thereof

tions was obtained by fine silk ligature, warm saline packs and by use of the electrocautery. No dressings were used on the operative incisions.

Originally it was planned to count the number of adhesions which formed following this procedure, but this method was found to be undesirable in that a true picture of the actual amount of serosa involved could not be obtained. Consequently, it was decided to estimate the area left bare of serosa after division of the adhesions (bare area).

Eleven to 35 days after the preliminary operation the experimental group was given Dicumarol by mouth to produce a lowered prothrombin activity. The animals in both groups were then operated upon through a new incision, the adhesions divided and the bare area estimated. The prothrombin activity of the animals in group two was kept at a low level for from four to 15 days and the animals were sacrificed eight to 21 days after lysis. The control animals were sacrificed nine to 32 days after lysis.

The animals in group three received the same preliminary operation as the other groups, but were given massive doses of Dicumarol before the gauze abrasion. With such severe depression of the prothrombin activity, hemostasis was almost impossible to obtain and no experiments regarding the reformation of adhesions were attempted. It is realized that a prothrombin activity this low would not be produced clinically. These experiments were done merely to ascertain the maximum effect one could expect from Dicumarol therapy.

Preliminary studies showed our dogs to have a normal prothrombin time of seven to eight seconds by the method of Quick¹⁶. The Dicumarol dosage was regulated in the same manner that it is done clinically. The initial dose was 100 mg. and additional doses of 25 to 50 mg. were given as indicated by the daily prothrombin activity. The dilution curve for prothrombin activity in the dog shows a much steeper climb at the lower percentages than does the human curve¹⁷. As a result the regulation of the prothrombin level in a narrow range is very difficult. At the time these experiments were planned, it was decided to keep the prothrombin activity between 10 and 30 per cent of normal¹⁸. This proved all but impossible and when the results were tabulated, the range was from 7 to 60 per cent.

RESULTS

Control dogs The total bare area after lysis of the adhesions resulting from the gauze abrasion ranged from 38.5 to 55.5 square cm. with an average of 46.2 square cm. (Table I). All of the adhesions were well formed, tough and showed no tendency to stretch. There was a preponderance of large sheet adhesions. Nine to 32 days later when the animals were sacrificed, the bare area which had reformed ranged from 68.5 to 198 square cm. with an average of 106.7 square cm. This amounts to an average reformation of 231 per cent in adhesive area. In most cases, the entire small bowel was bound firmly together in a ball. In all cases a loop or loops of small bowel were adherent to both operative incisions. In a few cases loops of bowel were adherent to the

liver, spleen, stomach or bladder. There was no gross difference in the character of number of adhesions present for nine days as contrasted to those that had been present for a longer period.

In the 12 operations performed on these animals, hemorrhage from the operative incision did not occur (Table II). There was a small superficial wound disruption in one animal.

TABLE I—*Reformation of Adhesions*

Group	of Dogs	Average Size of Bare Area at Lysis	Average Size of Bare Area at Sacrifice	Average Percentage of Reformation of Adhesions
Control	6	46.2	106.7	231.0
Experimental	14	45.8	11.3	24.6

Experimental dogs. The adhesions resulting from the preliminary operation were equal in all respects to those found in the control group. The bare area after lysis ranged from 38 to 54.5 square cm with an average of 45.8 square cm. This compares favorably with an average of 46.2 square cm in the controls. As stated above, the prothrombin activity at the time of lysis and in the postoperative period ranged from 7 to 60 per cent. This level was maintained for four to 15 days postoperatively. The animals were sacrificed eight to 21 days after lysis. Hemostasis in these animals was only slightly more difficult to obtain than in the control animals.

At the time of sacrifice, the bare area ranged from 2.5 to 15 square cm with an average of 11.3 square cm. This represents a 24.6 per cent reformation of the adhesive area as compared to the 231 per cent reformation in the

TABLE II—*The Effect of Dicumarol on Wound Healing*

Group	Number of Operations	Hemorrhage from Incision		Wound Disruption	
		No	Per Cent	No	Per Cent
Control	12	0	0	1	8.3
Experimental	14	3	21.4	2	16.7
Severely dicumarolized	6	6	100.0	5	83.3

control group. Actually, the difference between the serosal areas involved as marked as it is, by no means gives a true picture of the total gross change. The adhesions not only were smaller in size and fewer in number, but they were somewhat elastic and appeared poorly formed. Vascularization was noticeably less than in the controls. In only one instance was the small bowel adherent to the operative incision and in no instance was the spleen, liver or stomach involved. Lysis of these adhesions was more easily accomplished than in those resulting from the preliminary operation. The adhesions present in those dogs dicumarolized for only four days postoperatively seemed the same in all respects as in those animals dicumarolized for longer periods.

Slight postoperative oozing from the incision occurred in three or 21.4 per cent of these animals, but it ceased spontaneously with very little loss of blood. A minimal wound disruption occurred in two of these dogs. In each instance this was about a half inch long and extended only through the skin and subcutaneous fascia. In no instance was there disruption of the deeper layers. Aside from these two small disruptions, no difference was noted between the healing of the operative incision in this group and in the control animals.

Severely dicumarolized dogs. The prothrombin times in the animals of this group during operation and in the postoperative period ranged from 42 to 10,800 seconds or from 11 to less than 1.25 per cent prothrombin activity. Hemostasis was almost impossible to obtain and constant oozing from the operative site occurred. All of these animals died five to seven days postoperatively from hemorrhage.

At autopsy, the bare area ranged from none in one animal to 4.5 square cm with an average of 1.4 square cm. The previously abraded area appeared to be completely healed. There were varying amounts of blood in the peritoneal cavity and all of the animals had petechiae and ecchymoses scattered throughout the muscles and viscera. Wound disruptions occurred in five or 83.3 per cent. In no case did this involve all of the layers of the abdominal wall.

DISCUSSION

The results obtained show that Dicumarol is effective in reducing the extent of postoperative adhesions under the conditions of these experiments. Allowing a large error for the inaccurate manner in which the amount of serosa involved was estimated, the difference is still marked between the results in the control and treated groups. The control animals showed an average reformation of adhesive area more than nine times that of the treated animals. In addition to this, the reformed adhesions were much tougher and more extensive. We wish to point out, however, that therapeutic doses of Dicumarol did not prevent the reformation of adhesions in a single instance. In only one case was there an absence of adhesions following treatment with Dicumarol. This result occurred in an animal that expired on the fifth postoperative day from hemorrhage after receiving massive doses of the drug.

The results obtained here agree with those reported by Lehman and Boys^{1,4,5}. These authors were able to reduce the per cent of reformed adhesions from 156 in the control group of animals to 26 in the animals treated with heparin. Bloor *et al.*,⁷ on the other hand, observed less than an eight per cent decrease in the likelihood of adhesion formation when heparin was used. In their experiments on the redevelopment of divided adhesions, heparinization did not decrease the incidence over that observed in the control animals. This discrepancy in results is apparently due to the fact that Lehman and Boys reported percentages which referred to the number of adhesions developing in each dog, and not to the percentage of dogs in the series in which adhesions developed. On the other hand, Bloor *et al.* placed more

stress on whether an animal did or did not develop adhesions. If the amount of peritoneal involvement in both of these series is contrasted, the discrepancy becomes more apparent than real. In Bloor's control group, the average extent of serosal involvement increased from 6.9 cm. before lysis to nine cm. after lysis—a reformation of 130.4 per cent in adhesive area. In the treated group the extent of serosal involvement decreased from eight to six cm., a reformation of adhesive area amounting to 75 per cent. Thus, treatment with heparin produced a 55.4 per cent advantage over non-treatment. We believe that this interpretation of these results is permissible if it is kept in mind that the complications accompanying adhesions are probably influenced by the number and extent of the adhesions present.

One important point mentioned previously by others^{19,20} and illustrated by the work of Bloor *et al.* is that in a given group of individuals certain ones are more prone to form adhesions than others. This "adhesive diathesis"¹⁹ makes it difficult to evaluate the effect of an agent that diminishes the number of adhesions but does not prevent them.

The available data seems to indicate that the severity but not the incidence of postoperative peritoneal adhesions in dogs can be reduced by anticoagulant therapy.

It should be stressed that this is an experimental study in dogs only and that no recommendations regarding the application of this method in human beings is intended.

CONCLUSIONS

- 1 The results obtained with the use of Dicumarol for the prevention of postoperative peritoneal adhesions in dogs are presented.
- 2 In these experiments the use of Dicumarol reduced the extent of adhesions over 200 per cent.
- 3 Anticoagulant therapy for four days postoperatively appears to be as effective as for longer periods of time.
- 4 Heparin and Dicumarol appear to be effective in decreasing, but not in preventing postoperative peritoneal adhesions in dogs.

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THE EFFECT OF HEPARIN ON GELATIN SPONGE HEMOSTASIS*

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Evidence has accumulated that gelatin sponge† is an effective hemostatic in wounds of parenchymatous organs and large vessels^{1, 2} In many instances the continued patency of vessels on which gelatin sponge has been used is of utmost importance Although the incidence of thrombosis in vessels on which gelatin sponge has been used is probably no greater than those repaired by suturing, it might at times seem desirable to heparinize such patients However, the effect of heparin upon gelatin sponge hemostasis is not known The purpose of this investigation was to determine the effectiveness of gelatin sponge as a hemostatic agent in the presence of heparin

METHODS

In this experiment the effect of heparin on gelatin sponge was tested in two types of wounds in 250 Gm white rats The first type of wound was produced by exposing a lobe of the liver under ether anesthesia Using a razor blade a small slice of liver was removed The denuded surface, approximately one square centimeter in size, bled profusely though other experiments have shown that this type of wound ordinarily does not result in fatal hemorrhage The second type of wound used in this study was one of the vena cava An incision 5 mm long was made in the wall of the vessel in the lumbar region Such a wound results in fatal hemorrhage if left untreated In both the liver wound and the vena cava wound the gelatin sponge was applied after it was first soaked in saline solution After application firm pressure with the fingers was maintained for a period of five minutes

Suitable control groups of animals were studied to determine the effect of such wounds left untreated with gelatin sponge Other controls were observed when a celiotomy alone was done

Previous experiments had shown that 10 mg of heparin given subcutaneously in rats of the size indicated produced an incoagulable blood for longer than four hours Therefore when heparin was given, 10 mg were injected subcutaneously either before or 1, 24, or 48 hours following surgery

To determine the amount of bleeding subsequent to the administration of heparin, the animals were anesthetized four hours following heparin and the abdomen opened The site of application of the gelatin sponge plaque was inspected and the amount of bleeding into the peritoneal cavity measured If

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† Gelfoam (trade name of gelatin sponge) is manufactured by the Upjohn Co

the animal had lost one-third of its calculated blood volume, it was considered for this experiment to have had massive hemorrhage

RESULTS

The control group of eight rats showed that when a celiotomy was done and heparin was given one hour following operation, no intraperitoneal bleeding occurred. This indicated that such hemorrhage as might be found in later experiments where the liver and vena cava were incised could not be explained as hemorrhage from the abdominal wound.

When liver wounds were produced and patched with gelatin sponge massive hemorrhage occurred in all nine animals, if heparin had been given

TABLE I—Results

Type of Wound	No Gelatin Sponge		Gelatin Sponge	
	Number of Animals	% With Massive Hemorrhage	Number of Animals	% With Massive Hemorrhage
<i>Celiotomy wound</i>				
Heparin 1 hr. after surgery	8	0		
<i>Liver wounds</i>				
Heparin 1/4 hr. before surgery			9	100%
Heparin 1 to 4 hrs. after surgery	9	89%	8	75
Heparin 24 hrs. after surgery	5	0	13	20
Heparin 48 hrs. after surgery	10	0	31	16
<i>Vena Cava wound</i>				
No heparin	Immediate fatality			
Heparin 1 hr. after surgery			11	0
Heparin 24 hrs. after surgery			8	0
Heparin 48 hrs. after surgery			8	0

30 minutes before operation. This result is as expected, gelatin sponge presumably providing a substrate to strengthen a clot, will not be effective when the normal blood clotting mechanism is disturbed by large doses of heparin. If, however, the administration of heparin is delayed until after the liver wound has been produced and gelatin sponge applied, massive bleeding does not invariably occur. As expected, the longer the interval of time between operation and administration of heparin, the less is the incidence of massive secondary hemorrhage. Surprisingly enough, when heparin is given 24 or 48 hours after operation, bleeding is more likely to occur from liver wounds if gelatin sponge has been applied than if no patch of gelatin sponge was used.

When wounds of the vena cava were made the immediate application of a gelatin sponge patch was life-saving. In contradistinction to liver wounds, heparin was found safe when given as early as one hour following operation. In no animals where gelatin sponge was used and heparin given, 1, 24, or 48 hours following caval injury did massive bleeding occur. The results are summarized in the accompanying table.

DISCUSSION

It seems to be definitely demonstrated that in rats with vena cava injury a gelatin sponge patch will prevent massive hemorrhage and that heparin can be given safely within one hour of the application of the patch. Evidently, within a period of one hour the clot formed within and around the gelatin sponge is sufficiently firm and adherent to prevent bleeding even though the blood then be made uncoagulable by heparin administration.

With liver wounds of the type described, the results would indicate that bleeding may occur through and around a gelatin sponge patch if heparin is given as late as 48 hours after wounding. This can possibly be explained by assuming that bile exuding from the liver bed partially destroys or injures the previously formed clot and the slight bleeding that therefore occurs continues because the blood is now heparinized, and unable to form new clots. In such a wound the presence of gelatin sponge serves as a real impairment to healing. If the same wound is produced, but no gelatin sponge used, heparin can be given within 24 hours without subsequent bleeding, the omentum and adjacent viscera become adherent to the liver bed, sealing off the area so no bleeding occurs following heparinization.

CONCLUSIONS

1. Gelatin sponge is ineffective as an hemostatic in an already heparinized animal.
2. Animals with wounds of large vessels treated with gelatin sponge may be heparinized as early as one hour following injury without danger of hemorrhage.

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SARCOIDOSIS PRODUCING PORTAL HYPERTENSION*

TREATMENT BY SPLENECTOMY AND SPLENORENAL SHUNT

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MUCH ATTENTION HAS BEEN GIVEN to veno-venous shunts in the operative treatment of portal hypertension since Blakemore and Lord perfected the nonsuture, Vitallium tube technic of blood vessel anastomosis. The recent publications of Blakemore, Whipple, Blalock, Welch, and Linton and their colleagues afford an excellent summary of the currently established indications, techniques, and immediate clinical results of these procedures.

The etiologic aspects of portal hypertension have also been reviewed in these reports. Sarcoidosis of the liver, a subject which has been omitted from consideration, has apparently not been encountered as a cause of this condition.

The present communication is an account of our experience with splenectomy and splenorenal venous anastomosis in the treatment of the incapacitating symptoms of portal hypertension caused by sarcoidosis of the liver.

CASE REPORT

Mrs. E. C. (M. H. 62, 286), a Negro housewife 26 years old, was admitted to the Memorial Hospital on November 24, 1947, because of marked dyspnea and ascites. These symptoms were related to sarcoid infiltration of the liver and the spleen.

Her first admission to this hospital had occurred on November 12, 1943, three weeks after the onset of multiple joint pains, shortness of breath on slight exertion, and weakness of both legs. The details of her family history and past history were irrelevant. Her arms and legs were covered with discrete, indurated areas of pigmentation which also involved the trunk. Many shot-like lymph nodes, the largest 1 and 2 cm. in diameter, were encountered in the axillary, epitrochlear, inguinal, and femoral regions. The liver edge was palpable 8 cm. below the costal margin, and the spleen was enlarged to the level of the umbilicus. Routine examinations of the blood and of the urine disclosed no abnormalities. A chest film showed extensive, patchy lesions in the peribronchial areas, especially in both lower lobes. There were no roentgenographic changes in the bones of either hand. The presumptive diagnosis of sarcoidosis was established by histopathologic study of an excised cervical lymph node.

Trial of a variety of therapeutic measures in the out-patient department failed to prevent a gradual increase in the severity of the symptoms. Ascites was demonstrable after 18 months of treatment, and on two occasions hospitalization was required because

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of the progressive disability which followed. Thorough clinical and laboratory studies, throughout the period of illness, indicated that the only active foci of disease were present in the spleen and liver and possibly in the spinal cord. A state of total invalidism was believed to be at hand when accentuated symptoms led to the present readmission.

Physical examination The patient at this time was a thin young Negro woman with a strikingly enlarged, protuberant abdomen. Her weight was 135 pounds, and at the level of the umbilicus the circumference of her abdomen was 36 inches. A definite cyanosis of the nail beds was observed, and a slight degree of dyspnea was evident at rest. There were no apparent changes in the lesions of the skin or in the groups of enlarged lymph nodes which had previously been noted. The blood pressure was 110/72, the pulse rate was 88. The heart and lungs were normal. The liver edge extended to the umbilicus. The limits of the spleen were at the midline and at the left anterior superior iliac spine. There was moderate ascites. The knee and ankle jerks were absent. There was marked weakness of the extensor muscles of the thighs and lower legs, and there was moderate weakness of the other muscle groups. No peripheral edema was apparent.

Laboratory findings The red cell count was 3,400,000, the hemoglobin level 12.5 Gm, and the white cell count, 5,000. A differential count of 71 per cent neutrophils, 23 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophils was noted. The coagulation time was $3\frac{1}{2}$ minutes, the bleeding time was $2\frac{1}{2}$ minutes. The platelet count was normal. The prothrombin time was 52 per cent of the control. The plasma protein level was 6.61 Gm per 100 cc, representing 2.75 Gm per 100 cc of albumin and 3.86 Gm per 100 cc of globulin. With the bromsulfalein test there was 10 per cent retention in 30 minutes and 5 per cent retention in 1 hour. The cephalin cholesterol flocculation was 4 plus. The Congo red and galactose tolerance tests were negative. The concentration of the blood urea nitrogen was 20 mg per 100 cc. The urea clearance was 113 per 100 cc. The phenolsulfonphthalein test was normal.

A complete examination of the cerebrospinal fluid revealed no abnormalities. A chest film also indicated that there had been no changes in the peribronchial lesions.

Operation Splenectomy, with the creation of a veno-venous shunt, was recommended as the only therapeutic measure thought to offer any prospect of relief. Preliminary treatment by transfusions and by the administration of a diet low in fat and high in carbohydrate and in protein constituents was therefore instituted.

The operation was performed on December 11, 1947, (R. A. M.) with the patient under spinal and supplemental intravenous anesthesia. There was a moderate amount of clear ascitic fluid in the abdominal cavity. The visible serosal surfaces were smooth and glistening. The spleen was smooth, dark gray, and very firm to touch, it extended to the midline and to the level of the left anterior superior iliac spine. The liver was somewhat hob-nailed in appearance and also very firm to touch, its edge was at the level of the umbilicus. There were numerous retroperitoneal lymph nodes, the largest almost 3 cm in diameter. An accessory spleen was found which was about 6 cm in diameter. The uterus and ovaries were extremely atrophic. Moderately enlarged veins were observed in the gastrohepatic omentum and elsewhere in the portal area. The left renal vein was about 1.5 cm in diameter, the splenic vein about 10 mm in diameter.

The pressures in the coronary and middle colic veins were found to be equivalent to 175 mm of saline solution.

No unusual difficulty was experienced in the removal of the spleen. The pressure in the splenic vein was subsequently found to be equivalent to 180 mm of saline solution. In view of the appearance of the liver, the increased venous pressures were interpreted as evidence that the portal hypertension was of intrahepatic origin.

An end-to-side anastomosis of the splenic and renal veins, with preservation of the kidney, was therefore created, the presence of enlarged lymph nodes and plexuses of small blood vessels having been considered as a contraindication to the formation of a

portacaval shunt. The axial placement of a rubber-covered "McWhorter delicate model gallbladder forceps"* on the renal vein in the course of this procedure was found to be a very satisfactory method for securing partial occlusion of this vessel. The parallel closing of its very narrow blades assures an even grasp upon the vessel wall, and the flexibility of their structure results in minimal trauma to the intimal surfaces. Subsequent palpation of the anastomotic site indicated that the stoma was almost 1 cm. in diameter.

Additional determinations of the pressures were then made in various tributaries of the portal vein before the abdomen was closed. The lowest reading taken was found to be equivalent to 90 mm. of saline solution, but the accuracy of these results was considered questionable since no appreciable fluctuations of the column were associated with the respiratory movements.

The patient tolerated this procedure very well. During the operative period of approximately eight hours she received a total of 5,500 cc. of fresh citrated blood and 1,000 cc. of 5 per cent glucose in normal saline solution. She was returned to her bed with a blood pressure of 100/70 and a regular pulse rate of 110.

Postoperative course. A variety of complications developed in the postoperative period. Additional heparin was given to maintain a carefully controlled, prolonged coagulation time, but gross hematuria was noted ten hours after operation, in association with a rapidly falling blood pressure and a diminishing red cell count. The heparin was discontinued, and a total of 2,000 cc. of freshly withdrawn blood was given in the following five hours. The blood pressure was restored to normal levels by this treatment, and the subsidence of the hematuria was shortly afterwards observed. Abdominal distention in this period also made continuous gastric suction necessary. Dyspnea and cyanosis became evident 24 hours after operation. A bronchoscopic examination demonstrated an obstructing edema of the mucosa of the left lower bronchus which was attributed to the aspiration of gastric content during anesthesia. An oxygen tent afforded some relief from these symptoms. Considerable difficulty was then experienced in the management of the electrolyte balance, but with the administration of parenteral solutions a gradual return to normal was eventually observed.

A normal temperature was attained on the tenth postoperative day, and a soft solid diet, rich in protein constituents, was tolerated at this time. Fever reappeared a few days later, and in spite of massive doses of penicillin and streptomycin a subdiaphragmatic abscess developed on the left. An intravenous pyelogram demonstrated normal function and appearance of both kidneys. The abscess was incised and drained on January 17, 1948, with the patient again under spinal anesthesia. The cultures revealed strains of *Staphylococcus aureus* and *Bacillus coli* which were markedly resistant to the antibiotic agents. A superficial infection of the primary wound required drainage somewhat later, and a large decubitus ulcer finally appeared over the sacral area. This ulcer was excised on February 25, 1948, and the resulting wound was closed with a sliding flap of skin and subcutaneous tissue.

An uneventful convalescence then occurred. Healing progressed rapidly, the dyspnea and ascites disappeared, and the patient soon exhibited a ravenous appetite. The red cell count was 3,830,000, the hemoglobin level 12.5 Gm., and the white cell count 18,000. The prothrombin time was 100 per cent of the control. The plasma protein level was 6.39 Gm. per 100 cc. representing 2.45 Gm. per 100 cc. of albumin and 3.94 Gm. per 100 cc. of globulin. The cephalin cholesterol flocculation was 3 plus. With the bromsulfalein test there was 4 per cent retention in 30 minutes and no retention in 1 hour. Discharge from the hospital was granted on March 20, 1948, approximately 3½ months after operation.

Pathologic examination. The operative specimens included several retroperitoneal

* This instrument is supplied by V. Mueller and Company, Chicago.

lymph nodes, a wedge of tissue from the left lobe of the liver, the spleen, an accessory spleen, and a portion of the tail of the pancreas

The spleen measured 28 by 18.5 by 12 cm and weighed 2,250 Gm (Fig 1). There were scattered fibrinous adhesions and focal areas of hyalocapsulitis on the diaphragmatic surface of its capsule. It was abnormally firm. On section it was rusty brown in color, rubbery, and uniformly sprinkled with minute, somewhat reddish areas (Fig 2).

FIG 1

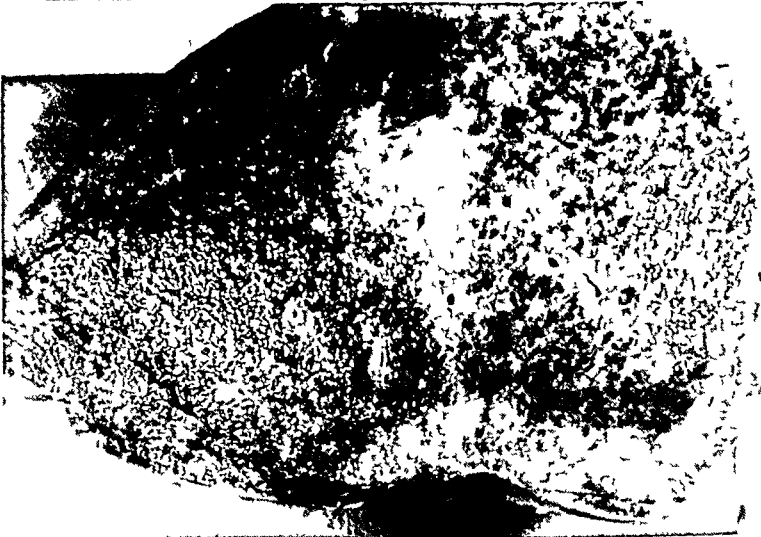


FIG 2

FIG 1—The appearance of the spleen (weight 2,250 Gm) immediately after its removal

FIG 2—A cut section of the spleen

Similar characteristics were shown by the accessory spleen.

The lesions of Boeck's sarcoid were beautifully demonstrated in the sections of the lymph nodes (Figs 3 and 4). Definite groups of epithelioid cells were present without evidence of giant cells or of caseation necrosis.

There were also definite and extensive sarcoid lesions in the spleen (Fig 5). Giant

cells of the Langhan's type were present, and "asteroid" inclusion bodies were occasionally noted. A fibrinoid necrosis was displayed in the central areas of many of the lesions, and in these instances a circumferential zone of partially necrotic, partially hyalinized and regenerating fibrous connective tissue was observed. There was no involvement of the intima of the veins.

FIG 3

FIG 4

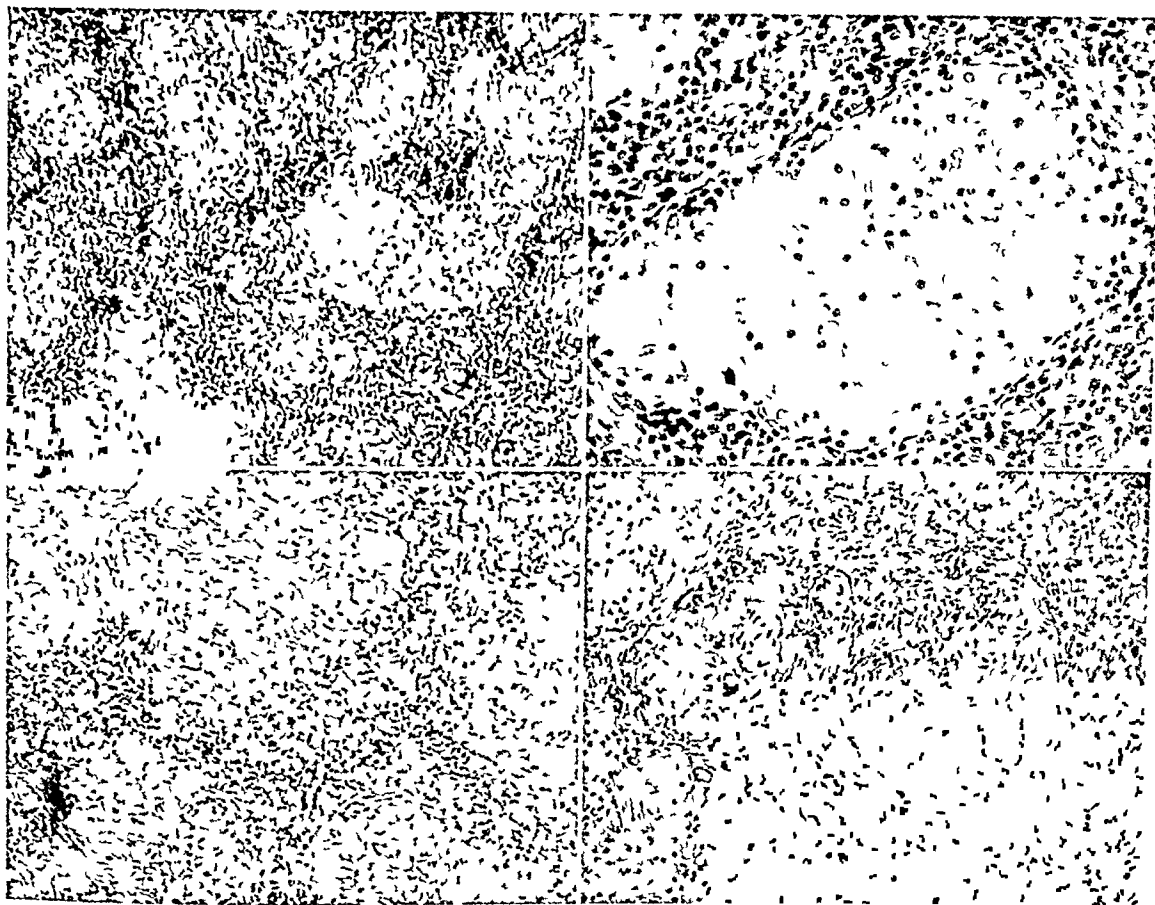


FIG 5

FIG 6

FIG 3—Sarcoid lesions in a retroperitoneal lymph node. The typical clusters of broad epithelioid cells show no evidence of giant cells or of caseation necrosis (x 60).

FIG 4—Detailed view of a sarcoid lesion in a retroperitoneal lymph node (x 175).

FIG 5—Sarcoid lesions in the spleen. The parenchyma is shown to be extensively involved (x 60).

FIG 6—Sarcoid lesions in the liver. There is a coalescence of the lesions about the portal triad shown in the center of the field (x 60).

The lesions in the tissue from the liver were found primarily about the tributaries of the portal vein in many of the portal triads (Fig 6). There was occasional involvement also of the central lobular veins. A striking infiltration of the walls of several of the larger, apparently sublobular veins was evident in other sections (Fig 7). No focal hemorrhages had occurred, although the lesions had encroached upon the intimal surfaces. A comparable infiltration has already been described by James and Wilson in the walls of the smaller splenic veins, but its occurrence in the walls of the hepatic veins is not known to have been previously reported. These findings serve to explain the mechanism of the portal hypertension in this case of sarcoidosis.

Special stains of all these tissues revealed no acidfast bacilli.

Subsequent course The patient has exhibited a very gratifying clinical response since her discharge from the hospital. She resumed her lighter household duties a few months postoperatively. As her ravenous appetite continued, her weight soon increased to 144 pounds, but the persistence of the weakness of her legs led her to accept a somewhat restricted diet. One year after operation the red cell count was 3,500,000, the hemoglobin level 14.5 Gm, and the white cell count 14,400. The plasma protein concentration was 7.10 Gm per 100 cc representing 3.00 Gm per 100 cc albumin and 4.10 Gm per 100 cc globulin. The cephalin cholesterol flocculation was 4 plus. With the bromsulfalein test there was 8 per cent retention in 30 minutes and 8 per cent retention in 1 hour. A chest plate showed slight clearing of the peribronchial lesions.



FIG 7—Sarcoid infiltration of the wall of a large hepatic vein ($\times 60$)

At the most recent visit, 18 months postoperatively, the patient weighed 130 pounds. The circumference of her abdomen was 24 inches. There was no evidence of ascites, dyspnea, or edema. The liver edge was palpable approximately 6 cm above the umbilicus. The weakness of her legs had not been changed. The patient was noticeably alert, active, and cheerful.

COMMENT

The extensive infiltration of the spleen and liver is of special interest in this case. Nickerson, Harrell, Longcope, and Reisner have observed that involvement of these organs frequently occurs in sarcoidosis, and Nickerson and Longcope have reported that splenectomy has been performed in certain instances of this disease in the erroneous belief that the preoperative signs and symptoms were evidence of Banti's syndrome. The serious obstruction of the venous blood flow in the liver in the case recorded here is believed to be an unusual manifestation of these lesions. Their periportal distribution was undoubtedly a most important factor in the production of the ascites. The spleen is also thought to be the largest yet described in sarcoidosis.

It is evident that ascites has rarely been encountered as a complication of this disease. Reisner has described a peritoneal effusion in one case in his series, but he has attributed this finding to sarcoid infiltration of the serous membranes.

The indication for operative intervention in the case reported here was the presence of the progressive, incapacitating ascites. It is realized that sarcoidosis is a generalized disease in which the clinical manifestations vary in accord with the extent and distribution of the lesions, and it is also recognized that the occurrence of spontaneous remissions or exacerbations makes the prognosis difficult in the individual case. The patient in this instance was observed, however, for a period of four years, and, except for its progression in the spleen and liver and possibly in the spinal cord, the disease in her case was believed to have become quiescent. She was obviously being reduced to a state of invalidism, and operative treatment was thought to offer

her the only possibility of relief. The venous shunting operations are not advised in sarcoidosis unless the primary disease has become stationary and incapacitating ascites or bleeding from esophageal varices has occurred. The prognosis should be guarded in spite of operation.

SUMMARY

A case of portal hypertension which was caused by sarcoidosis of the liver is reported, and a histopathologic explanation of the mechanism of this syndrome in sarcoidosis is presented.

Treatment by splenectomy and spleno-renal venous anastomosis is advised in this condition when the primary disease has entered a quiescent phase and when evidence of bleeding or of incapacitating ascites has occurred. A satisfactory result has been obtained in the case reported here 18 months postoperatively.

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OBSTRUCTION OF THE INFERIOR VENA CAVA ABOVE THE RENAL VEINS*

REPORT OF A CASE WITH RECOVERY OF RENAL FUNCTION
FOLLOWING THE USE OF THE ARTIFICIAL KIDNEY

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IT HAS BEEN STATED¹ that occlusion of the inferior vena cava above the level of the renal veins is almost universally fatal. Most of the reported human cases have been instances of sudden obstruction in a previously patent vessel. Keen³ has pointed out that where the occlusion is gradual, adequate collateral channels can form, and although some degree of renal damage may occur, the kidney function is good enough to maintain life. Many workers have shown that ligation of the inferior vena cava above the renal veins carries a very high mortality in experimental animals.^{1, 2, 6} Death occurs due to kidney failure with uremia. The renal lesion is a form of lower nephron nephrosis, the damage being chiefly in the tubules, while the glomeruli remain relatively intact.⁸ This fact is important because the tubules have great powers of regeneration and if life can be maintained long enough for a collateral circulation to develop there is an excellent possibility that renal function will be restored to normal. Until recently, a patient with complete renal shutdown could survive only a limited time before death occurred due to uremia. Kolff⁴ has recently developed a method of clearing the blood of toxic waste products. This machine, the "artificial kidney," utilizes the principle of dialysis across a semi-permeable membrane, and has proved its value in cases of uremia due to reversible lesions of the kidney.⁶ With such an apparatus the period of survival can be indefinitely prolonged. There are no reports in the literature of its use in vena caval obstructions, but on theoretical grounds it should be of great value.

The collateral circulation in obstruction of the inferior vena cava is chiefly through the vertebral plexus, the lumbar veins and the suprarenal, testicular or ovarian veins. Other channels may develop in the anterior abdominal wall and by communications with the portal venous system. There is a greater collateral on the left side than on the right, because the embryonic channels may be present as small vessels which can enlarge if the need arises. On the right side, all the embryonic vessels have been incorporated into the vena cava and no vestigial channels are present. In addition, the testicular or ovarian vein enters the renal on the left side and offers another anastomotic pathway which is absent on the right. Thus, theoretically, the left kidney would have a better chance of developing an adequate venous return (Fig. 1).

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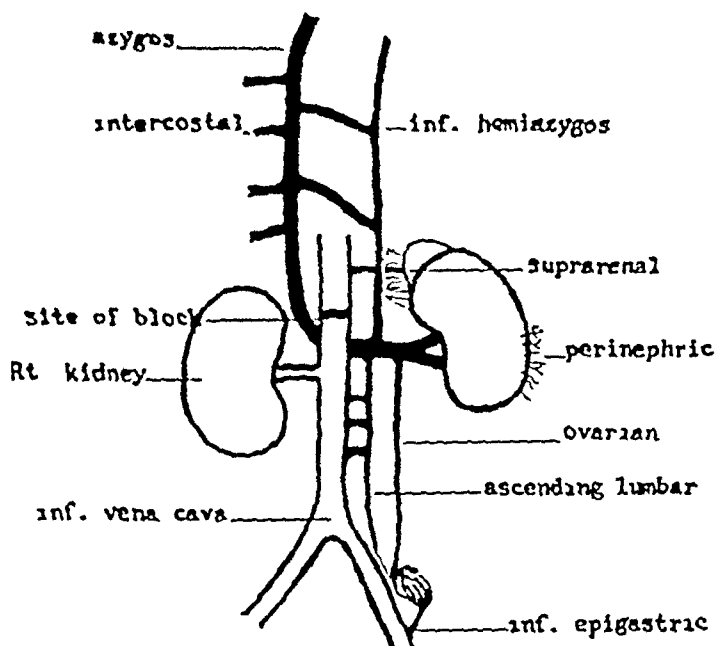


FIG. 1—Diagram showing a greater collateral circulation may be present on the left side than on the right, because of the presence of potential embryonic channels



FIG. 2—Right subcostal incision extending from the loin to the linea alba

CASE REPORT

F R, female age 55, was admitted to the Royal Victoria Hospital, Sept 19, 1948, for investigation of pain in the right upper quadrant and right loin of one year's duration. Examination revealed a palpable subcostal mass and roentgen ray visualization of the gallbladder showed cholelithiasis. Laparotomy, October 28, did not confirm this diagnosis. A large retro-peritoneal tumor was found displacing the liver and gallbladder anteriorly. A biopsy was taken and the incision closed.

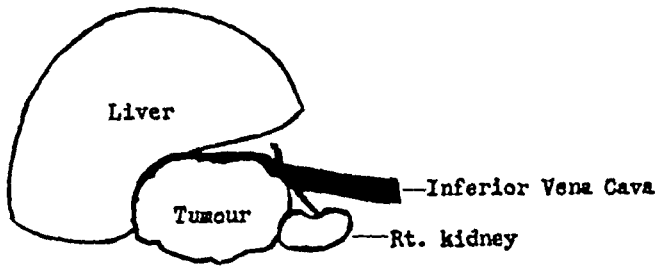


FIG 3—Diagram of vena cava, stretched over the surface of the growth in ribbonlike fashion, compressing the vessel to a great extent



FIG 4

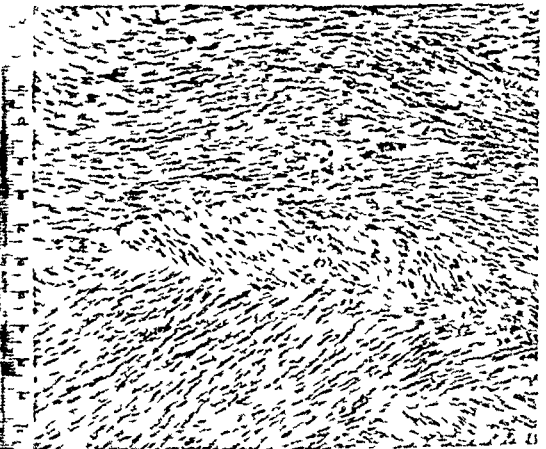


FIG 5

FIG 4—Gross specimen, benign fibromyoma

FIG 5—Microscopic section of gross specimen

The pathologic report established a diagnosis of benign fibromyoma, and it was decided to attempt removal of the tumor.

On Oct 13, 1948, operation was performed through a right subcostal incision extending from the loin to the linea alba (Fig 2). The tumor was freed from the surrounding structures and was found to be adherent to the inferior vena cava and the right kidney. The vena cava was stretched over the surface of the growth in ribbonlike fashion, compressing the vessel to a great extent (Fig 3). The right kidney was removed, and in freeing the growth from the vena cava a segment of the vessel wall was excised. The opening was sutured with fine silk, but the lumen of the vessel was narrowed to such an extent that no

OBSTRUCTION OF INFERIOR VENA CAVA

blood passed the constriction, and the vena cava was collapsed above it. The area of constriction was just above the level of the renal veins. The patient's condition was too precarious to warrant any further procedure, and it was decided to take a chance on the collateral circulation. The wound was closed with interrupted silk, and a drain inserted into the right loin (Figs 4 and 5).

Postoperatively she recovered well from the effects of the surgical procedure but was anuric for seven days. Her NPN gradually rose to 172 mg per 100 cc and her creatinine

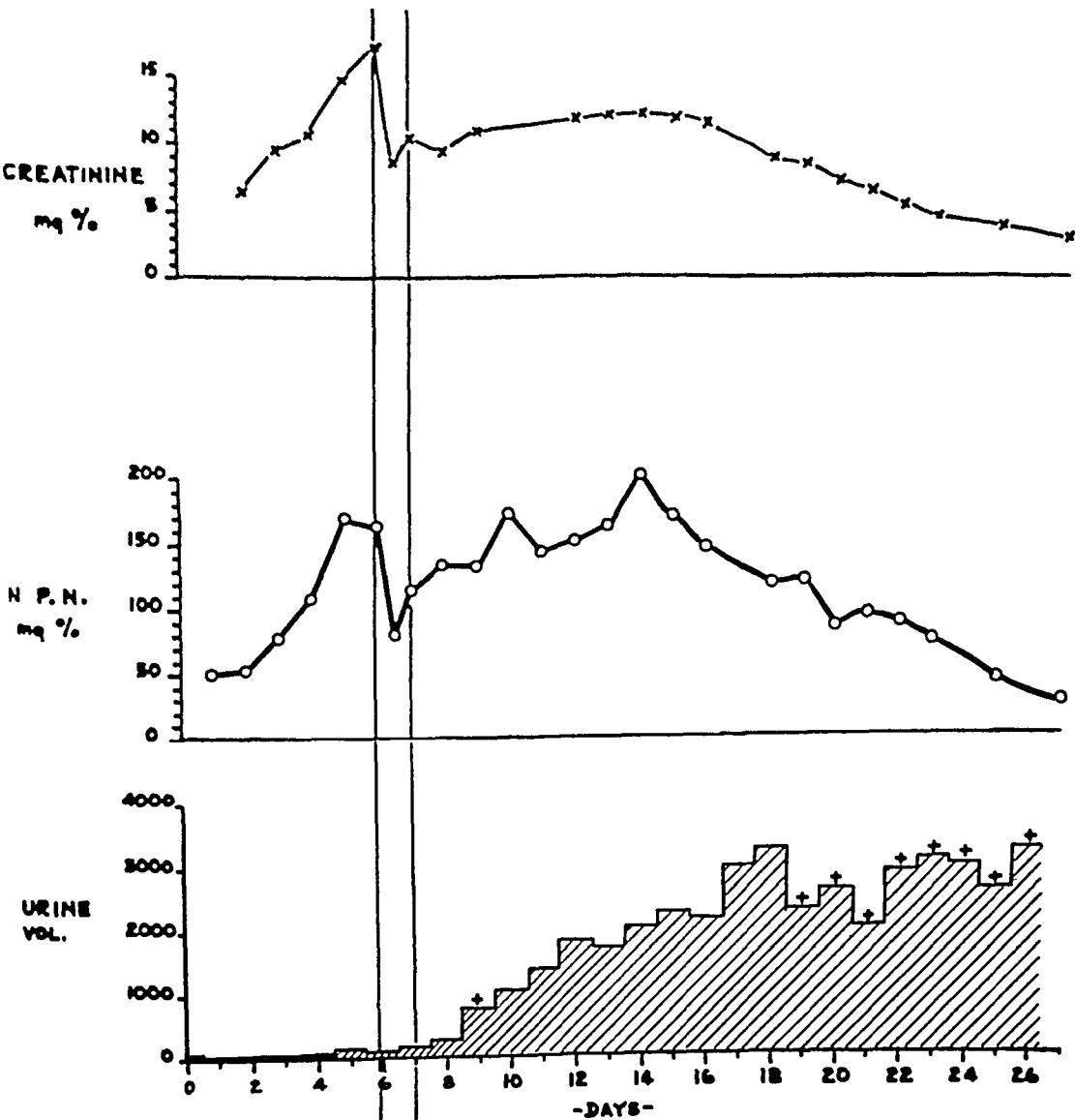


FIG 6—Postoperative chemical changes of blood

to 17.2 mg per 100 cc. On Oct 20, 1948, she was connected to the artificial kidney and a six-hour dialysis was carried out. During the treatment the NPN dropped to 83.5 mg per 100 cc and the creatinine to 8.8 mg per cc. The following day the NPN rose to 119 mg per 100 cc but the patient was subjectively improved and her urinary output increased to 180 cc. In the following days her urinary output gradually returned to normal. The NPN remained elevated until November 10 when it reached a normal level (Fig 6).

Postoperative renal function tests show adequate function in the solitary kidney. The patient has moderate dependent edema of the left leg but is otherwise well.

COMMENT

This case presents several unique features. The large retro-peritoneal tumor had undoubtedly caused gradual compression of the inferior vena cava. The collateral circulation must have developed to some extent, but it was not sufficient to enable the kidney to function in the immediate postoperative period. The artificial kidney was of great value in improving the patient's condition at a critical time. The rise in NPN following dialysis has been observed in many of our previous cases. It represents a flooding of the bloodstream with waste products which have accumulated in the tissues. As a rule it is not accompanied by clinical symptoms of uremia.

During the period of anuria the blood chemistry and urine findings were typically those of a lower nephron nephrosis. The patient has apparently made a complete recovery and regained adequate kidney function.

Since the vena cava was sutured and not divided the possibility exists that some blood flow was resumed through the normal channel.

The important point is that venous occlusion existed for a period and uremia resulted. The recovery was due to the development of an adequate venous return either through collateral channels or the vena cava. Since a partial obstruction had existed for some time, it is likely that the collateral pathways were well developed.

SUMMARY

1. A case is presented in which the inferior vena cava was obstructed above the level of the renal veins.

2. After an initial period of anuria this patient regained renal function and recovered.

3. The artificial kidney was of value in combatting uremia while waiting for the collateral circulation to develop.

4. The renal lesion in vena caval obstruction is a form of lower nephron nephrosis and apparently recovery can occur under favorable circumstances.

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EVACUATION OF TRAUMATIC EXTRADURAL HEMORRHAGE FROM THE POSTERIOR FOSSA*

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HEMORRHAGE of extradural origin into the posterior fossa is rarely encountered on a clinical basis. A small number of cases of this type of hemorrhage have been discovered at necropsy but clinically cured patients are few in number. A careful review of the literature has shown five previous cases of extradural posterior fossa hemorrhage with cure to be reported. The work of Wharton⁶ in 1901, on 70 cases of venous sinus wounds of the brain, includes eight cases of extradural posterior fossa hemorrhage. In five of these cases, the source of bleeding was from the Torcular Herophili and in three cases the bleeding was from the lateral sinus. Only one of the cases of Torcular hemorrhage lived and none of the cases of lateral sinus hemorrhage successfully survived surgery. Guidjian and Webster,³ Kessel,⁴ Turnbull,⁵ and Coleman and Thomson,¹ have each reported one case of extradural posterior fossa hemorrhage successfully evacuated by operation. Considering the small number of cases reported and with the feeling that early recognition may aid in the successful outcome of this condition, we are adding one more case to the five previously mentioned. In the patient about to be discussed, the hemorrhage was primarily in the posterior fossa and the principal source of bleeding was from the Torcular Herophili.

CASE REPORT

R. R., a 26-year-old white male was involved in an automobile accident at approximately 3 A.M. on September 9, 1948. While driving home, he fell asleep at the wheel of his car which careened into the post of a low retaining wall. At 4 A.M. the patient walked into the local police station in a dazed condition, remembering his name but none of the details of the accident. With the exception of an abrasion in the occipital area, the patient showed no other evidence of injury. On admission to the Chestnut Hill Hospital a short time later, the blood pressure was 150/90, pulse 100, and respirations 24 per minute. The pupils were equal and reacted to light and accommodation. At the time of examination it was noted that the Babinski sign was negative bilaterally.

By 8 A.M. the blood pressure had risen to 180/100 with a pulse of 70. The patient complained of severe occipital headaches and did not appear well oriented. He responded with purposeless movements to painful stimuli and required sedation with paraldehyde at 11:45 A.M. By 2 P.M. the blood pressure had increased to 190/104 and the pulse risen to 112 per minute. There was no evidence of paralysis but the mental picture showed increasing drowsiness and confusion. It was decided that the patient's signs of increased pressure were probably on the basis of intra-cranial bleeding, and he was transferred to the Neurosurgical Service of the Hospital of the University of Pennsylvania at approximately 4:30 P.M. On admission to the University Hospital he showed pronounced stupor and it was difficult to obtain a satisfactory neurological examination. However, the left

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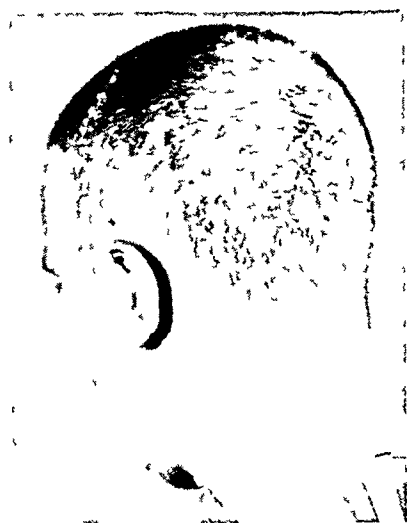


FIG 1—Left posterior craniotomy wound at time of discharge from hospital

pupil appeared slightly larger than the right, there was a left VI nerve weakness and the patient showed slight evidence of a right hemiparesis. It was decided that the patient might well have an acute subdural or possibly extradural hemorrhage, and he was immediately taken to the operating room.

A left temporal burr hole was placed (G M A), and showed a thin layer of blood approximately 1 mm thick over the cortex amounting to 3 or 4 cc of fluid. An occipital burr hole was next placed on the left side and revealed a thick extradural clot pushing the dura away for a depth of about 2 cm. In order to locate the bleeding point and evacuate the clot, a flap was turned down over the left lateral sinus, using the originally placed burr holes as limits for the anterior and posterior limbs of the flap. On turning back the flap, it became apparent that we were dealing with a large posterior fossa hemorrhage. It was primarily on the left but also present to a limited extent on the right side and had extended up over the tip of the left occipital lobe. Approximately 3 to

4 ounces of clotted and liquid blood were removed by suction and several oozing points in the lateral sinus were controlled by the Bovie current. The main source of bleeding was a

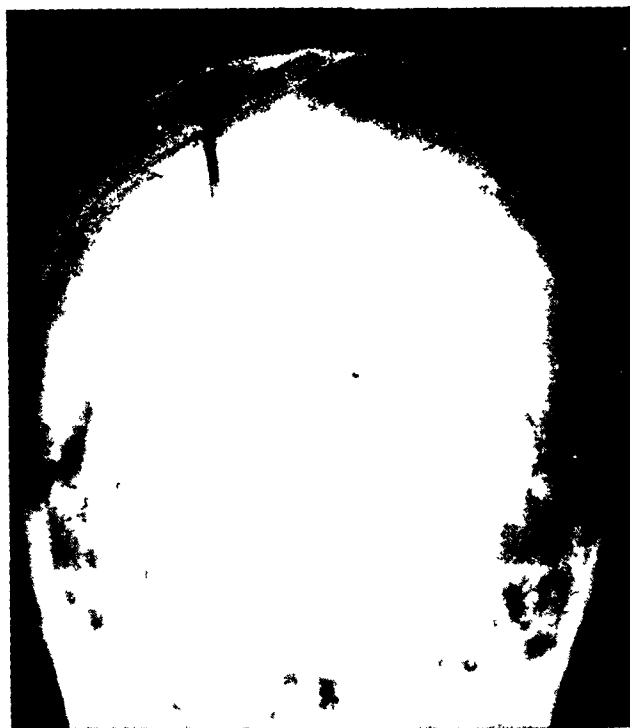


FIG 2—Postoperative skull film showing fracture in left occipital bone

small tear in the Torcular Herophili. This bleeding was stopped by the use of gelfoam and the wound closed in layers. A Penrose drain was left in the posterior fossa coming out through a stab wound drainage hole posterior to the flap. At the conclusion of the procedure the patient had begun to respond although he still was not conscious enough to reply to

questions. The following morning he appeared fairly alert and was able to eat a full-sized meal. Thereafter his convalescence was uneventful. The drain was left in place for 48 hours and the patient permitted to be ambulatory on the third postoperative day. At the time of discharge from the hospital 11 days after admission, he was neurologically negative and able to return to his previous job of bartender (Fig. 1).

Postoperative skull films on the patient showed a deep linear fracture line extending down into the occipital bone on the left side of the foramen magnum (Fig. 2).

DISCUSSION

The successful case of posterior fossa hemorrhage of extradural origin, reported by Gurdjian and Webster³ was due to a traumatic tear in the lateral sinus. This patient straightened up after leaning forward and accidentally hit the back of his head against the sharp edge of an iron pipe, with resultant perforation of the skull. The patient became stuporous over a period of 36 hours and, at operation, an epidural hematoma of about two ounces was removed from the posterior fossa.

In Wharton's⁶ series of cases, there were three instances of hemorrhage originating from the lateral sinus and bleeding into the posterior fossa, all of which proved fatal. There was one case of operation with recovery, among the five cases of Torcular hemorrhage. This case was that of a 24-year-old youth, struck on the back of the head by a dump car on August 31, 1886. The patient was brought to the Hospital of the University of Pennsylvania and found to have sustained a compound fracture of the occipital bone. The skull was trephined and the depressed fracture elevated by Professor Ashhurst. When the largest fragment was removed, "just over the junction of the lateral and superior longitudinal sinuses, there was a gush of venous blood which was quickly controlled by packing the wound with antiseptic gauze." The patient recovered, and five months later was readmitted to the University Hospital with typhoid fever which proved fatal. Necropsy showed a well organized thrombus over the Torcular.

These two cases, reported by Gurdjian and Webster³ and Wharton,⁶ have two points in common. They were both cases of acute hemorrhage and they were both due to a torn sinus following depressed skull fracture.

The case of Coleman and Thomson¹ was that of a nine-year-old child who fell and suffered mild trauma to the back of the head without unconsciousness. Roentgenograms of the skull showed a midline linear fracture extending into the rim of the foramen magnum. Approximately 60 hours after the trauma the child was hypotonic and areflexic. At operation a bilateral extradural cerebellar clot was removed, followed by complete recovery.

Turnbull⁵ described an interesting case of chronic extradural cerebellar hematoma. The patient suffered a fall on the ice with a resultant blow to the left forehead, ten months prior to coming to surgery. Roentgenograms of the skull revealed no evidence of fracture. However, she showed pronounced cerebellar signs and a ventriculogram revealed a moderate internal hydrocephalus. At operation, a hematoma, the size of a golf ball was found over

the right cerebellar hemisphere. The patient made an uneventful postoperative recovery.

Kessel⁴ has described the case of a 24-year-old girl who fell from a bicycle striking the back of her head. A roentgenogram of the skull revealed no fracture but the left half of the lambdoid suture showed separation. No cerebellar signs were noted but the patient had three tonic seizures in the 60-hour period following admission and preceding surgery. At operation a large extradural clot was removed from over the left cerebellar hemisphere. This was followed by gradual but complete recovery.

These cases all reveal slightly varying etiology, but the type of roentgen-ray picture may be divided into three groups. The cases of Turnbull⁵ and Kessel⁴ showed no fracture at all, but Kessel's showed a slight separation of the left half of the lambdoid suture. Wharton's⁶ case, and that of Gurdjian and Webster,³ both revealed compound depressed fractures. In our own case, and that of Coleman and Thomson,¹ simple linear fractures were found to run down toward the foramen magnum.

Likewise, the neurological picture varied considerably, and only two patients showed signs of cerebellar involvement when examined preoperatively. There are a number of fatal cases reported, in which the traumatic instrument itself, such as a bullet, icepick, etc., actually produced the tear in the dural sinus following perforation of the bone. However, none of those occurring into the posterior fossa has recovered.

Most recently, Gordy² has again stressed the importance of attaching localizing significance to overlying superficial scalp abrasions following mild head trauma. Certainly the case we have just reported presented a mild scalp abrasion over the occiput which was not considered significant at time of examination. This is of increasing importance when it is realized that there may or may not be suggestive roentgen-ray evidence for this type of lesion and that cerebellar signs are only occasionally present.

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MASCULINIZING TUMOR OF THE OVARY†

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MASCULINIZING TUMORS OF THE OVARY are admittedly rare. These generally fall into two main groups: arrhenoblastoma, and a heterogeneous group classified as "virilizing lipoid cell tumors" by Barzilai.³ The first case of arrhenoblastoma was reported by Pick²⁰ in 1905, and it was not until 1933 that a case was reported as such in America.²³ However, in 1921 Moots¹⁵ described a 27-year-old patient with "lateral partial glandular hermaphroditism." This woman was masculinized and had a tumor of the left ovary. When the "fibroblastic sarcoma of embryonic testis" of the left ovary was removed, she became refeminized. The microscopy as described, and the clinical picture designate this as an arrhenoblastoma. Baldwin and Gafford¹ in 1936 reviewed the literature and could find only 33 cases. The most recent review, that of Iverson⁸ brings the total to 94 cases. The total number of "virilizing lipoid cell tumors" recorded in the world literature is 21, these, too, are summarized by Iverson.⁸

While the pathologic diagnosis of arrhenoblastoma based on histologic study has occasioned little difficulty in the past (Iverson⁸), the case to be reported indicates that this need not be and is indeed not always so. The chief function of this paper, apart from adding a new case to the literature, is to emphasize the difficulty in making a diagnosis, especially when this diagnosis is based solely on histologic examination of the tumor.

CASE REPORT

Mrs. M. S., a 34-year-old white Polish woman, was first seen at home late at night on November 23, 1943. She complained of abdominal pain, and this was her first such attack. The pain, centered in the left lower abdominal quadrant, had come on suddenly, and was of several hours duration. There had been no nausea or vomiting, nor had the patient had any bowel disturbances, urination had not been excessively frequent. Menstruation had been normal and regular, but had ceased suddenly two years previously. For several years she had had normal cohabitation, but had not conceived. She had two normal children, 18 and 14 years of age, both living, and had had one spontaneous miscarriage prior to the birth of her first child.

On examination, temperature, pulse and respiration were normal. The patient was a robust woman physically, her head and neck and chest were negative. Her abdomen was moderately tender and in the left lower quadrant there was a palpable tender mass about the size of a large orange. Bimanual examination revealed that this mass was attached to the left adnexae, the right adnexae appeared normal, the cervix was not tender to touch, nor was the uterus enlarged. A diagnosis of ovarian cyst with probable twisted pedicle was made. Hospitalization was advised, but was refused.

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The following morning the pain was more severe and the patient was admitted to the Beth-El Hospital. She now appeared to be acutely ill. The abdominal pain was more generalized, there was more resistance to palpation, and the cyst could not be felt as distinctly. Temperature was 100°, pulse 94, respiration 20, and blood pressure 125/80. Her red and white cell counts were 4,200,000 and 12,000 respectively, with 68 per cent polymorphonuclear leucocytes and 22 per cent lymphocytes, hemoglobin was 85 per cent. Her urine had a specific gravity of 1.020, was yellow in color, showed no casts, a few epithelial cells and a few white cells, and was negative for both albumin and sugar.

She was operated upon under spinal anesthesia with the preoperative diagnosis of a left ovarian cyst with twisted pedicle. When the peritoneal cavity was opened, a bloody fluid in which floated clumps of granular reddish-gray neoplastic tissue was observed. The left ovary had been replaced by a cystic mass approximately 10 cm. in diameter which had perforated. There was no walling off and no matting. The pelvic region was filled with this bloody fluid. The uterus appeared smaller than usual, almost infantile, and the right ovary was shrunken and firm. Both tubes and ovaries were removed and the fluid aspirated from the peritoneal cavity. The abdomen was closed in layers. The patient had a normal uneventful postoperative course. The wound healed well and she was discharged on the tenth postoperative day. Several days after the operation, the microscopic slides were examined and the diagnosis of arrhenoblastoma was made (M. J.).

On the basis of this new information the patient and her husband were carefully questioned and the patient was re-examined. The following additional data was obtained. As indicated above, the patient had stopped menstruating two years previously, she had not conceived for many years despite the fact that no contraceptives had been used. Sex life had been otherwise normal and there had been no change in libido. The patient had always been strong and robust and no change had been noted in that regard. However, her voice had changed, it had become deeper and husky, she had also become more hairy. Examination revealed no marked hirsutism, there were sparse hairs on her upper lip, the pubic hair, however, was definitely of the male type, straight and coarse and extending to the umbilicus, the legs and arms felt firm, the hips were narrow and lacked female contour, her breasts were small, flat, and devoid of fat, the labia majora appeared small, the clitoris, on the other hand, was enlarged and firm. A clear cut defeminization had apparently occurred.

Because of the widespread intraperitoneal dissemination of neoplastic tissue when the mass ruptured, we suggested postoperative radiation therapy. The patient refused such therapy or any other medication.

More than five years have now elapsed since the operation. She feels well and has no complaints. Together with her son, she operates a 104-acre farm. She had gained about 40 pounds in weight but during the past two years since working on the farm she lost about 25 pounds. Her libido is unchanged and sex life has continued normally. Physically there appears to be a distinct refeminization. Her voice is softer. Her breasts became rounded, firm and prominent, but in the past year have become pendulous. The pubic hair is now curly and there is less hair above the pubis. There is no hair on the face. The clitoris is much smaller and softer.

PATHOLOGIC REPORT (M. J.)

The specimen was composed of a mass approximately 7 cm. in diameter which was almost completely filled with a very friable grayish tissue and considerable recent blood clot. There were several irregular rents. The outer surface was smooth, glistening and felt firm. Attached to it was a fallopian tube 5 cm. long, patent and grossly unaltered. The smaller ovary appeared atrophic when compared with the tube, although there were no apparent gross fibrous changes, the surface was smooth. On section corpora albicantia were distinct and no cysts were observable.

MICROSCOPIC DESCRIPTION

Sections of the smaller ovary showed no histologic changes. These contained numerous corpora albicantia, but no corpora lutea, cysts or hemorrhagic areas, nor were any fragments of luteum-like cells present. Both tubes were histologically unaltered.

Sections of the mass and of the loose tissue accompanying the specimen showed a rather narrowed but highly cellular structure which appeared to be of three main types. In all of these, however, the basic cell was round or cuboidal or low columnar and small. All had rather large, central or slightly eccentric, rounded vesicular nuclei. These cells were arranged in short or long solid cords surrounded by rather cellular (spindle cell) or mod-

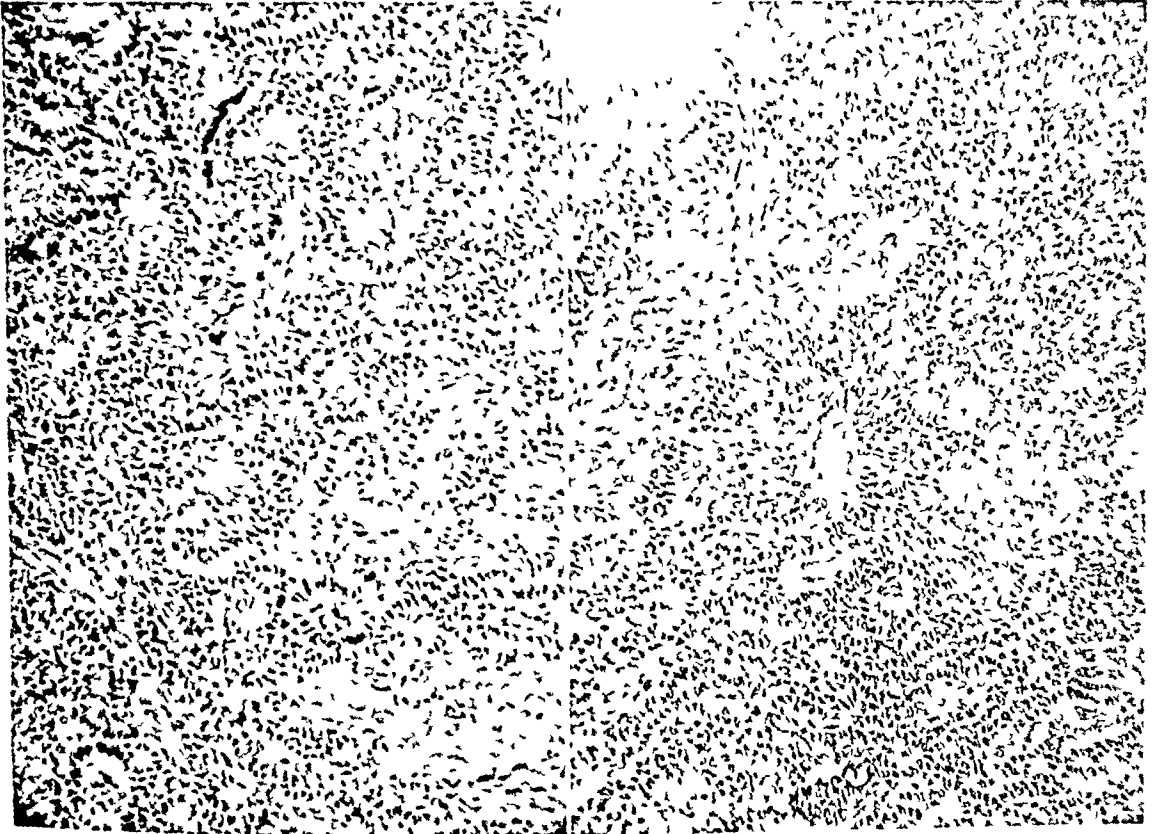


FIG 1

FIG 2

FIG 1—Low power photomicrograph of tumor showing tubular structures resembling testicular tumors.

FIG 2—Low power photomicrograph showing anaplastic and spindle arrangement of cells, and an area resembling the so-called Call-Exner body.

erately adult fibrous tissue, in numerous places distinct tubular patterns with well developed tubules lined by cuboidal or columnar cells with basally-polarized nuclei interspersed these cords. This tissue was rather sharply demarcated from the very small amount of fibrous ovarian tissue (stroma) surrounding it, here and there, however, the neoplastic cells extended almost to the capsular surface. There was considerable necrosis in the deeper portions of the tumor, with recent hemorrhage, scattered between the tumor and the surrounding ovarian stroma were present clumps of old blood pigment and some phagocytes. In a few places one found small cystic folliclelike structures containing homogeneous acidic substance and somewhat reminiscent of the so-called Call-Exner bodies seen in the mature granulosa portion of the graafian follicle. No other follicular elements were present nor were the surrounding tumor cells as definitely arranged in such areas as is noted in instances

of granulosa cell tumor. These areas were interpreted as being accidental features due to tumor degeneration. Scattered sparsely through the sections were isolated large vacuolated cells, suggestively lipoid-containing, these cells very occasionally occurred in small clusters. Numerous sections from various portions of the tumor failed to disclose any cytologic or histologic elements other than those noted above. There was no suggestion of any teratomatous elements. The structures described above are shown in the accompanying photomicrographs (Figs 1-6). On the basis of the gross and microscopic findings the mass was diagnosed as an arrhenoblastoma.

DISCUSSION

Although the slides described above were seen by several pathologists in this city, no questions as to classification as an arrhenoblastoma were raised.

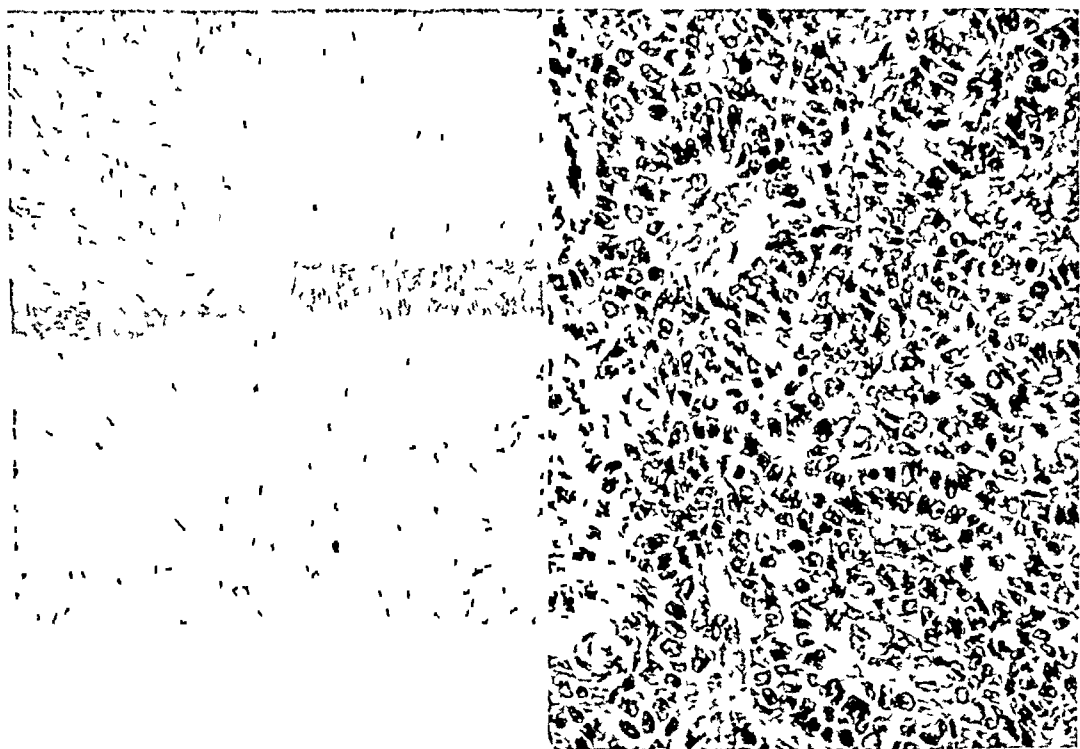


FIG 3

FIG 4

FIG 3—Low power photomicrograph showing intermediate stages between Fig 1 and Fig 2. Section contains a large amount of stroma.

FIG 4—High power photomicrograph of tumor through the tubular area.

Then Dr Nathan Mitchell, our (M J) successor as pathologist at the Beth-El Hospital, in a routine examination of the hospital files, suggested that the tumor was of the granulosa cell variety. The slides had previously been carefully studied by Doctors Paul Klempere⁹ and Sadao Otani¹⁰ of Mt Sinai Hospital, New York, and by Dr Herman Bolke⁵, pathologist to the Brooklyn Cancer Hospital. All three had concurred in the diagnosis of arrhenoblastoma. Dr Klempere and Dr Otani suggested, on the basis of a case of their own, that the tumor be studied further for evidences of teratomatous

growth As indicated above, no such elements were found upon very exhaustive examination

In view of the opinion of Dr Mitchell, to which he adhered on morphologic grounds even after being made aware of the clinical picture, slides were submitted to a prominent tumor pathologist who thought that the tumor was granulosa in type This pathologist has recently again studied the slides with full knowledge of the subsequent opinions He still adheres to his original diagnosis of granulosa cell tumor, and requests that his name not be published

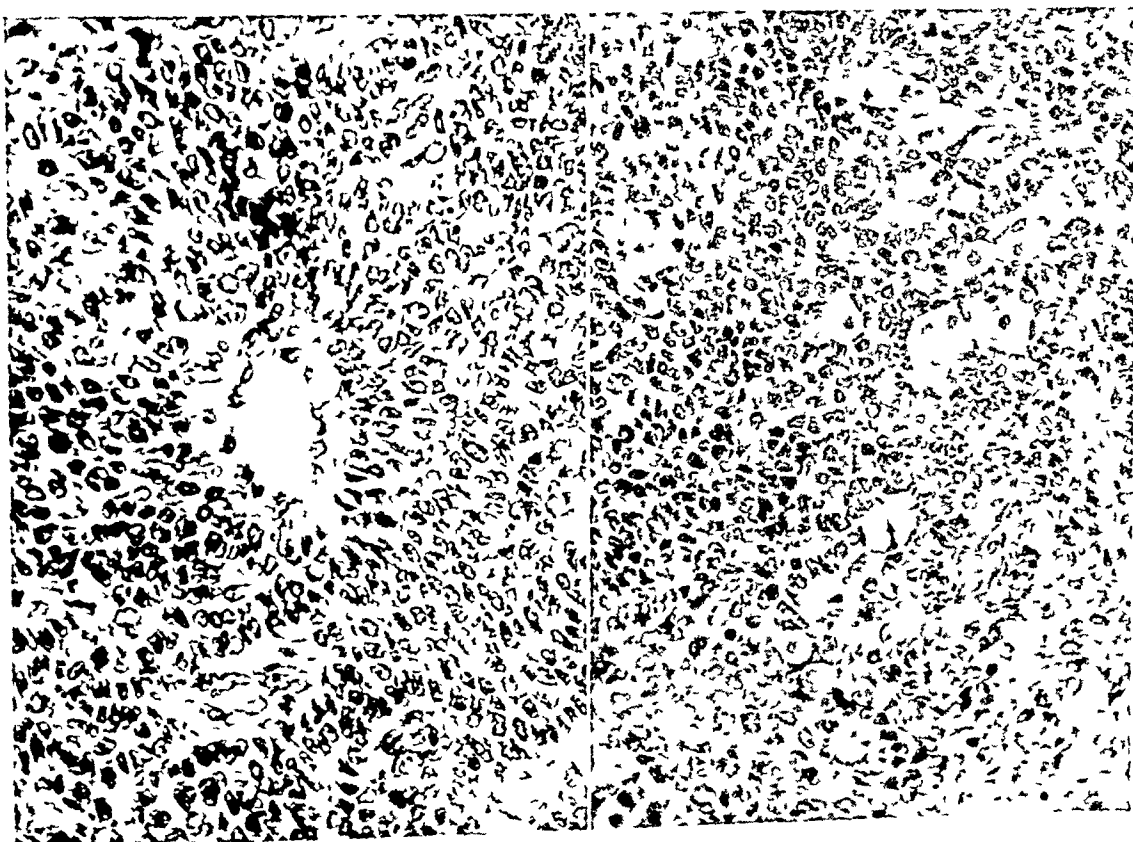


FIG 5

FIG 6

FIG 5—High power photomicrograph of the tumor through the anaplastic and spindle cell areas Note the absence of palisade cellular arrangement around the homogeneous material in the area suggesting the so-called Call-Exner body and the degenerative features of cells in the vicinity

FIG 6—High power microphotograph of the tumor showing the generally discrete lipid-like cells Note total absence of lutein-body formation

He suggested that the opinion of Dr Andrew Marchetti, then of Cornell University Medical College, be sought Dr Marchetti¹² unequivocally classified the tumor as an arrhenoblastoma

The slides were then sent to Dr Robert Meyer¹³ who said "This is a clear granulosa cell tumor, so called labyrinthine type" No reasons for this opinion were advanced Dr Meyer is credited with having originated the term "arrhenoblastoma" from the Greek "arrhenas," which means "male", postulating that the tumor arises from cords of male cells persisting in the medullary portion of the ovary from early gonadogenesis, they having failed for some

reason to undergo the normal process of atrophy. The slides were then examined by Dr. Emil Novak, who concurred in the diagnosis of granulosa cell tumor, stating¹⁶ "not only the morphology of the cells, but also their arrangement in little clusters, suggesting primitive follicles, as well as the presence of Call-Exner bodies, would leave no doubt of the diagnosis. The cylindromatous tendency is very marked in some areas, so that the cells are reduced to long thin columns which suggest arrhenoblastoma, but pictures of this type are not unusual with granulosa cell tumor. I do not see any evidence of arrhenoblastoma in this section, in spite of the fact that the history indicates a definite masculinization." With this latter statement, Dr. Novak was probably referring to page 417 of his monograph on *Obstetric and Gynecologic Pathology*¹⁷ where he says, "The fact remains, however, that the clinical history is of the greatest value to the pathologist in the microscopical examination of these tumors."

Two years later, Dr. Novak asked for further data in this case, which had been restudied and was now classified as an arrhenoblastoma. In reply to a query from Dr. Mitchell, Dr. Novak said, "I can only say that further study of these slides by all the members of the Ovarian Tumor Committee (of the Registry of Ovarian Tumors of the American Gynecological Society) led to the diagnosis of arrhenoblastoma, which of course matches up very well with the clinical history of the case. It may seem strange that there should be any difficulty in distinguishing between granulosa cell tumor and arrhenoblastoma, but the fact is that there are certain cases in which the histologic picture is almost identical in many areas. As a matter of fact, one of the members of our committee felt that this tumor would better be considered a gynandroblastoma in which both types of tissue are present, although the effects are practically always masculinizing. However, we have definitely classified this tumor in our Registry as an arrhenoblastoma."¹⁸

These diverse opinions on identical material recall the experience of Cole⁶ with tumors of the stomach, pointing up the profound limitations of morphology. These should make the clinician wary of regarding the pathologic-morphologic diagnosis as an absolute yardstick, and should raise serious questions as to the malignancy of tumors classified by such criteria, particularly in a group which is still so small. Thus, though our case showed evidence of peritoneal implants at the operating table, and the histology suggested malignant characteristics, more than five years have now elapsed without the slightest suggestion of cancer, this despite the absence of any additional therapy designed to hold a malignant tumor in check. Others have had similar experiences with so-called malignant ovarian tumors.¹¹ The implication of those concurring in the diagnosis of granulosa cell tumor is that this type of tumor may be associated with masculinizing changes. As pointed out by Seyle²² such a combination is exceptional. When this combination does exist, a very small arrhenoblastomatous area occurring in a tumor otherwise predominantly granulosa cell in character may give rise to virilization. This could only be detected by serial sectioning and examination of the entire tumor, a pro-

cedure not generally carried out in cases so reported. In addition, in such a case the masculinizing features do not ordinarily subside after ablation of the tumor as they characteristically do in instances of arrhenoblastoma.²¹ Whenever virilizing changes occur with granulosa cell tumor, the "granulosa cells" either become thoroughly luteinized, in many instances to the point of resembling corpora lutea (Novak,¹⁷ page 402) or show large masses of lipoid cells in the interstitial stroma. It has been postulated by Novak and by Iverson, that masculinization is a function of these lipotropic cells. While vacuolated lipoid containing cells were found in the stroma in our case, the so-called granulosa cells did not show lipotropic changes. In addition, although the masculinizing features in our patient were rather prominent and receded after the removal of the tumor, the stromal lipotropic cells were relatively few in number, inconspicuous, discrete and never in masses of lutein or adrenal-like character. The so-called Call-Exner bodies in our material we interpret as evidence of degeneration of the tumor tissue, no unequivocal follicles were found. As pointed out by Ewing,⁷ "In a substantial proportion of ovarian tumors as they actually occur, the diagnosis is largely a matter of arbitrary decision on the part of the observer." If this is so, in the present state of our knowledge we prefer, for reasons of simplicity and clarity, to adopt the nomenclature of Buirows² who designates as "arrhenoma" all testoid producing, and as "theeloma" all folliculoid producing tumors, irrespective of their structure, especially in view of the statement of Seyle that "it is impossible with the histologic methods now available, to determine the origin of these tumors with certainty."

Iverson's study, pointing out that masculinizing tumors may arise from totipotential ovarian elements, as well as the diversity of classification of these tumors by competent pathologists based on what may be minor and perhaps inconsequential differences in morphology, indicates that further knowledge in this field will come about only when the clinician preoperatively becomes more conscious of these tumors. More detailed studies of the patient's hormonal physiology, and of the hormonal content of the tumor proper, as has been done in instances of testicular tumor by Beilly, Kurland, and Jacoby,⁴ should be undertaken. Kanter and Klawans¹⁰ studied the electrolyte and nitrogenous bodies in the urine and in the blood, and also made hormonal determinations in the urine and on parts of the tumor in a case of arrhenoblastoma, but thus far there have been few clinical studies of hormonal physiology in connection with masculinizing tumors of the ovary.

SUMMARY

1. A case of masculinizing tumor of the ovary is reported. Despite rupture into the peritoneal cavity with consequent dissemination of neoplastic material, the patient, after removal of the mass, has remained free of untoward symptoms for more than five years, with no additional medication. Refeminization has also occurred.

2 The difficulties of pathologic classification on morphologic ground alone are discussed with reference to this specific case. A plea is made for a greater awareness of these tumors preoperatively, which, in turn, may lead to more numerous and detailed study of the hormonal physiology of the patient. It is also suggested that the tumor itself be assayed hormonally in order to arrive at a better correlation of clinical findings, hormonal physiology and pathologic anatomy.

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APPENDICEAL CALCULI, THEIR PATHOLOGIC AND CLINICAL SIGNIFICANCE^{*}

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Although fecal concretions are commonly found within the appendix, calculi are quite unusual. Bunch and Adcock¹ found only one in 2,000 appendices. The rarity of this disease and its clinical significance justify reporting an additional case. Moreover, the diagnosis in this case was made preoperatively.

CASE HISTORY

R. W. S., a 21-year-old white male, entered the hospital on January 12, 1948, with the chief complaint of pain in the right lower quadrant of the abdomen of two weeks' duration. Following discharge from the Army in April, 1947, he lost 23 pounds. Two weeks prior to admission the patient had intermittent attacks of right lower quadrant pain lasting a few hours at a time. The pain was dull, non-radiating, and unrelated to meals, defecation, or urination. Past and family history were non-contributory.

Physical examination revealed a thin, sluggish patient. His temperature was 98 degrees F, pulse 80, and his respiratory rate 20. The abdomen was scaphoid, soft, and slightly tender to deep palpation over McBurney's point, but rebound tenderness was not elicited. Rectal examination was negative.

Laboratory studies revealed a white-cell count of 4,100, with 43 per cent neutrophils, 53 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophils. The red-cell count was 4,100,000 with 140 Gm of hemoglobin. The urinary sediment contained occasional erythrocytes and granular casts. The urine culture was negative. Typhoid and paratyphoid agglutinations were negative.

Roentgen ray examination of the chest was within normal limits. Barium enema films showed partial filling of the appendix and calculi in the right lower quadrant. Retrograde pyelography revealed a normal urinary tract. The roentgenologic diagnosis was "chronic (stasis) appendix."

On January 19, 1948, an axillary lymph node was removed under local anesthesia. The pathologic report was lymphoid hyperplasia. At laparotomy five days later, the appendix was found lying over the pelvic brim, non-adherent to the adjacent structures. Palpation revealed that it contained several stones, including a large one near its base. Appendectomy was performed after a thorough exploration failed to reveal any other abnormalities. The postoperative course was uneventful. He was free of abdominal pain and had gained six pounds when seen eight months later.

The pathologic report indicated that the appendix was 8 cm long and varied from 1.5 to 3.7 cm in width, with a dilatation a short distance from its base. Within the appendix were seven calculi, the largest one being 2.5 by 2.0 by 1.6 cm. This stone was roughly cuboidal in shape with several nodular projections on its surface. The other stones varied in size and shape. The mucosal surface of the appendix was slightly edematous and grey with pinkish discoloration. The wall was thickened and there was

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congestion of the serosal vessels. Microscopically the mucosal glands were intact. The submucosa was replaced by dense fibers of collagenous connective tissue which had encircled the lymphoid follicles and obliterated the inner layer of the muscularis. The pathologic diagnoses were appendiceal calculi and chronic healed appendicitis.

Comment. The giant calculus in this case measured 80 cc, the fourth largest reported in the literature. A complete tabulation of the reported cases is shown in Table I.

TABLE I—Appendiceal Calculi Reported in the Literature Indicating the Size of the Individual Stones and the Eventual Outcome of the Pathologic Process in Each Instance

	Dimensions	Volume	Number of Calculi	Perforation	Size of Appendix
Tripodi and Kruger ¹⁷	2.5 cm diameter	8.2 cm	1	No	5 x 2.5 cm
Thomas ⁷	3 x 1.5 cm		1	Yes	
Pilcher ¹⁸	2.75 cm diameter	10.8	1	No	6.5 x 3.3
Bunch and Adcock ¹	2.70 cm diameter	10.2	5	No	3.5 x 1.4
Packard ¹⁹	A 2.4 x 1	8	2	Yes	7.0 x 1.5
	B 1.5 x 0.6				
Shahan ²⁰	1 x 0.7		23	No	
Jackman ¹⁶	A 0.8 x 3.14		1	Yes	
	B 0.5 x 3.14		1	Yes	
Guido ²¹	1 x 2 x 2.5	5.0	1	No	
Shelley ²	Boomerang shaped				
	small		1	Yes	8 x 3 cm
Vermooten ⁸	2 x 1 x 1.5	3.0	4	Yes	7 x 3.5
Muller ²³	4.5 x 1.5				
Rigollot, Simonnot, and Saissi ²⁴	3 x 1.8				
Jacobs ²⁵	2.5 x 3			Yes	
Douglas and Le Wald ¹⁴	A 2 x 1.5		1	Yes	
	B 1.6 x 1.2		1	Yes	
Wells ¹²	3.25 x 0.25		3	Yes	
Downes ²⁶	Filbert sized				
Levi ²⁷			1	No	
Albert ¹⁰			4	No	
Lowenberg	2.5 x 2.0 x 1.6	8.0	7	No	8 x 2.7 cm

Pathologic Physiology. Appendicitis may be due primarily to inflammatory change or to mechanical factors. Appendicopathy of the mechanical type may be initiated by any of the following foreign bodies: "shot, pins, glass, eggshell, enamel, bristles, hair, wood, gallstones, pin worms, cherry stones, grape seeds, raspberry seeds, caraway seeds, fig seeds, etc.,"² bilharzia,³ and clam shells.⁴ Any of these may form the nucleus of a fecalith or a calculus.

When a bolus of feces becomes impacted within the appendix, calcium salts from the mucous glands in the crypts of Lieberkuhn may be deposited upon the concretion. The appendix becomes thickened and the stone laminated by repetition of this process.⁵ If there is interference with circulation or lymphatic drainage of the appendiceal wall during any of these episodes perforation may occur.⁶ In nine of the 17 cases reviewed perforation took place and some of these went on to a fatal termination. The presence of a calculus associated with acute appendicitis presages a graver prognosis.

since 80 per cent of the reported cases have been complicated by perforation or abscess formation⁷ On rare occasion the process goes still further and the stone extrudes itself through a sinus in the right lower quadrant¹²

Chemical Analysis Appendiceal calculi were analyzed by Maver and Wells⁸ who studied 25 stones varying from 5 to 10 mm in diameter They state "about one-fifth of the material was organic residue, mostly vegetable fiber, indicating that some part of the appendiceal concretions at least, comes from the cecum Probably the rest of the concretion is deposited from the

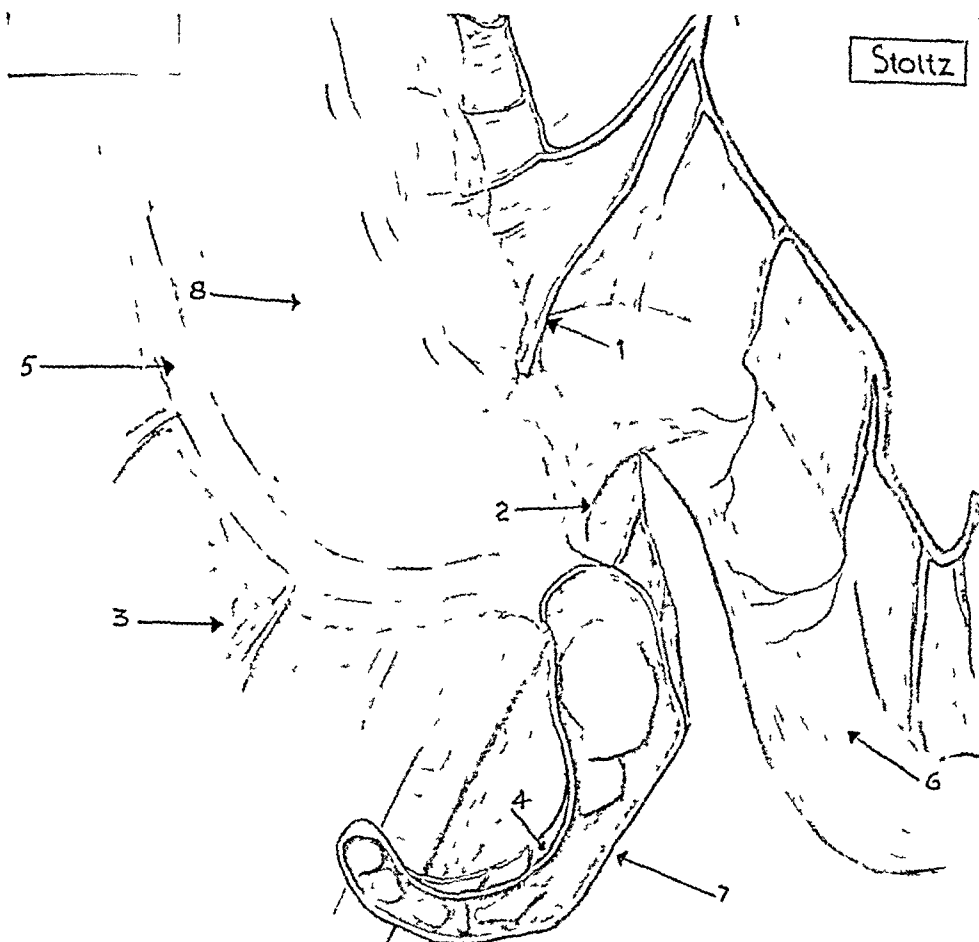


FIG 1—A reconstruction showing the appendix and the calculi as they looked at the time of laparotomy (1) Ileo-colic fossa, (2) Ileo-cecal fossa, (3) Retro-cecal folds, (4) Mesoappendix, (5) Tenia coli, (6) Terminal ileum, (7) Appendix, (8) Cecum

walls of the appendix since the bowel secretions are known to contain much fatty material and calcium" They found the calculi to contain inorganic material 25 per cent (chiefly calcium phosphate), organic residue 20 per cent (chiefly vegetable fiber), and fat soluble substances 50 per cent (coprosterol, soaps, and cholesterol) Vermooten⁹ analyzed a laminated stone and found it to contain bile, cholesterol, and siliceous material (mainly calcium phosphate)⁹

Differential Diagnosis The following diseases in addition to appendicitis must be considered in the differential diagnosis (1) ureteral^{11 13} renal¹⁰ or

vesical stone, (2) cholecystitis and cholelithiasis¹⁰, (3) gall stone ileus, (4) phlebolith, (5) calcified mesenteric nodes, (6) retained barium, (7) calcified dermoid of the ovary, (8) calcified appendix epiploica, (9) appendiceal foreign body¹⁵

Diagnostic procedures which have proved most helpful include spot roentgenograms¹⁴ of the right upper and lower quadrants,¹⁶ cholecystography, gastro-intestinal series and barium enema, as well as intravenous and retrograde pyelography. Pneumoperitoneum has been used as an aid when the diagnosis



FIG 2

FIG 2—A retrograde pyelogram showing the kidneys and ureters filled with radiopaque material, and in the right lower quadrant, just below the pelvic brim a calculus is visualized.



FIG 3

FIG 3—A lateral roentgenogram of the appendix after its removal.

could not be made conclusively.¹⁰ Extraperitoneal exposure of the ureter was performed when the location of a calculus could not be determined.¹¹

SUMMARY

1. A review of the reported cases of appendiceal calculi is presented, together with a description of one additional case which was diagnosed preoperatively.

APPENDICEAL CALCULI

- 2 The etiology and composition of appendiceal calculi is briefly discussed.
- 3 The clinical significance of these calculi in terms of perforation and prognosis is emphasized

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A COMBINATION PROBE, DILATOR AND IRRIGATOR FOR COMMON DUCT SURGERY*

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THE MULTITUDE of instruments available for exploration of the common bile duct indicates that none fills all requirements in a satisfactory manner

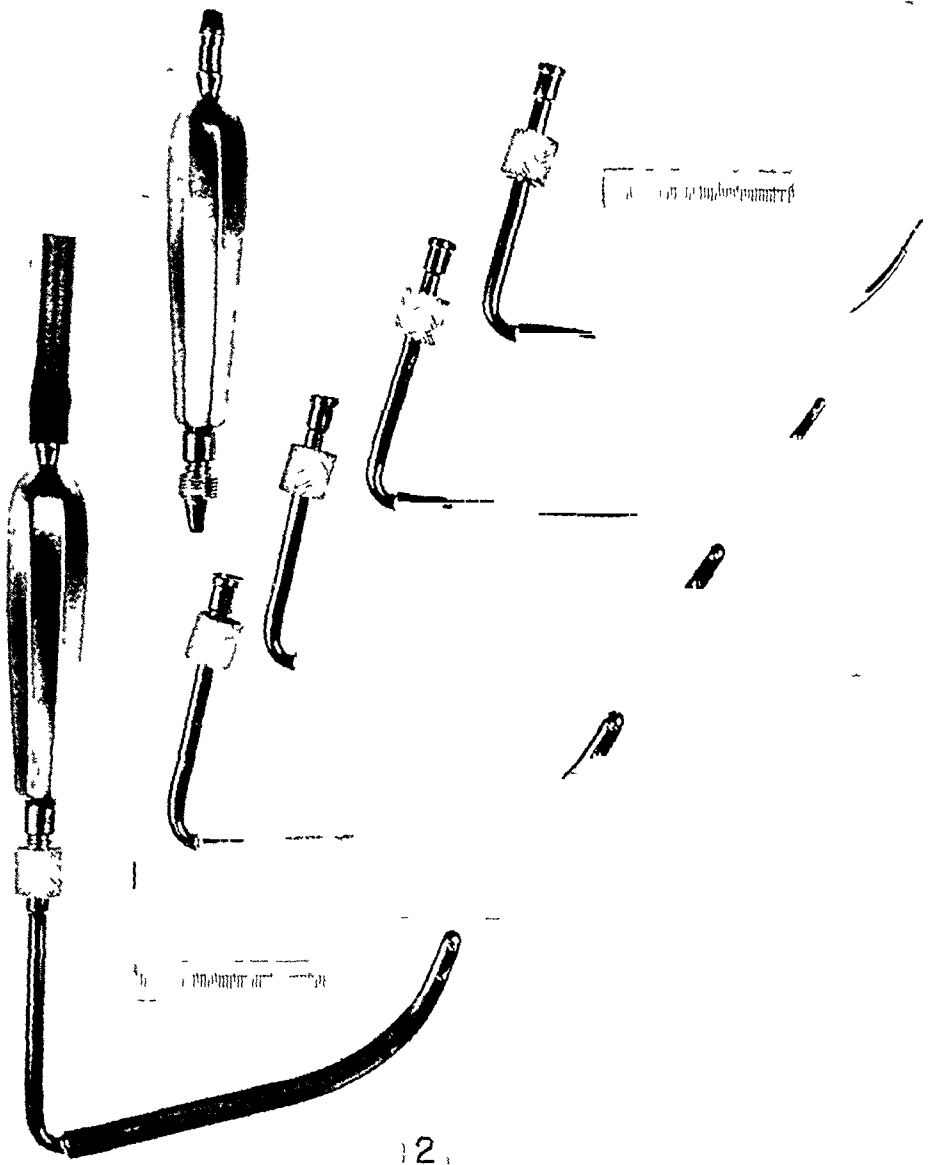


FIG 1—The Archibald instrument with detachable handle and graded-sized probes

FIG 2—The instrument assembled

* Submitted for publication December, 1948

The late Dr Edward Archibald devised an instrument which has been in use in the Royal Victoria Hospital for the past 15 years. It has proved to be so simple and efficient that it is considered worth while to publish a brief description.

The instrument consists essentially of a hollow handle with a series of detachable hollow probes of graded sizes. These are designed to fit the curve of the common duct and are perforated so that irrigation may be carried out. The device can thus be utilized as a probe, irrigator or dilator (Figs 1 and 2).

The probes are sizes 12F, 17F, 23F and 29F. These have proved to be the most useful in practice and they provide a good range for dilatation of the

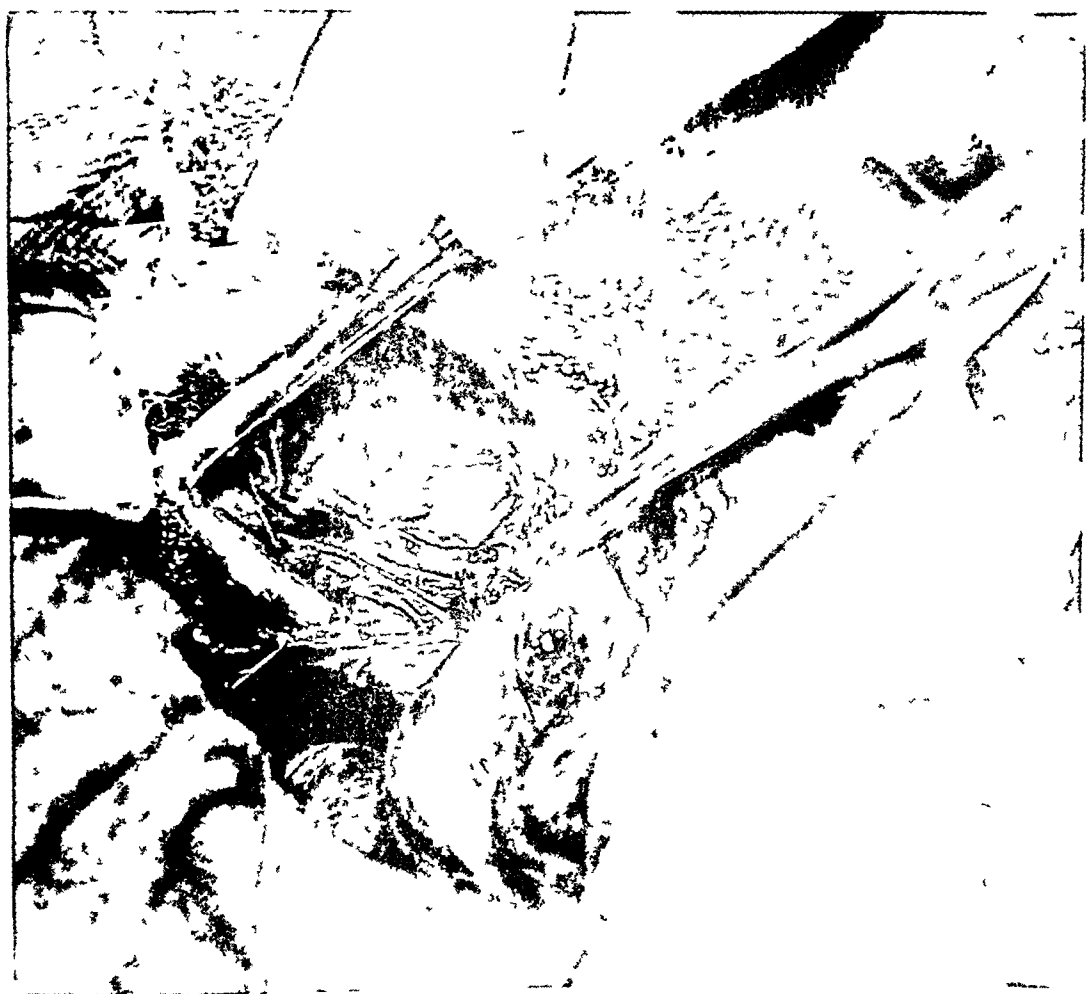


FIG 3—The probe in use in exploration of the common bile duct

sphincter of Oddi. The neck of the probe is angulated 75° in order to clear the costal margin when introducing the instrument into the duct. The length is 7 cm from neck to tip.

In the average case the probe can be introduced with the handle attached but in obese patients it is easier to insert the appropriate probe and screw on the handle in situ (Fig 3).

A bulb syringe can be attached to the handle and saline irrigated through the probe.

It is usually possible to pass the smallest size into the duodenum and if the sphincter of Oddi is tight or the seat of a stricture it can be gently dilated with the successive sizes. We have found this instrument to be far superior to any other which has been used in the Royal Victoria Hospital. It has stood the test of time and appears to be a worth-while addition to the armamentarium of biliary-tract surgery.

STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC., REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912, AS AMENDED BY THE ACTS OF MARCH 3, 1933, AND JULY 2, 1946 OF ANNALS OF SURGERY, published monthly at Philadelphia, Pa., as of November 1, 1949

State of Pennsylvania }
County of Philadelphia } ss

Before me, a Notary Public in and for the State and county aforesaid, personally appeared J. R. Arnold, who, having been duly sworn according to law, deposes and says that he is the Treasurer of the ANNALS OF SURGERY and that the following is to the best of his knowledge and belief, a true statement of the ownership, management (and if a daily paper, the circulation), etc., of the aforesaid publication for the date shown in the above caption, required by the Act of August 24, 1912, as amended by the Acts of March 3, 1933 and July 2, 1946, embodied in section 537, Postal Laws and Regulations, printed on the reverse of this form, to wit:

1 That the names and addresses of the publisher, editor, managing editor, and business managers are: Publisher, J. B. Lippincott Company, E. Washington Square, Philadelphia, Pa.; Editor, Dr. John H. Gibbon, Jr., Chairman Editorial Board, 1025 Walnut St., Philadelphia, Pa.; Managing Editor, Loraine Stauffer, E. Washington Sq., Phila. 5, Pa.; Business Manager, Laurence S. Whyte, E. Washington Square, Philadelphia 5, Pa.

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[Signed] J. R. ARNOLD

Affirmed to and subscribed before me this 3rd day of October, 1949
[Seal]

HARRY J. BEARD

(My commission expires March 5, 1953)

Editorial . . .

DIVERTICULITIS OF THE COLON

DIVERTICULOSIS OF THE COLON is a common condition among individuals of both sexes over the age of 50. It is now being recognized that a variable degree of diverticulitis occurs in almost all of these cases. Fortunately for the purposes of surgical treatment, in a very large percentage the diverticula are confined to the sigmoid and lower descending colon. In the cases of diverticulitis requiring surgical therapy this is equally true, over 85 per cent of the lesions being confined to this area. Thus, complete excision of the local lesion may be carried out if surgical intervention should be required.

Although the disease most often follows a fairly definite course, the future of any individual case is quite unpredictable. Thus the progress of the inflammatory changes, although usually slow, may be rapid, complications, which ordinarily occur late, may appear at an early stage. Therefore, once recognized, each case must be followed carefully by the general physician and re-examined at regular intervals.

For many reasons the medical profession at large has adopted a rather inert and ultra-conservative attitude towards the surgical therapy of this condition. This attitude often results in the continuance of palliative treatment long after definite danger signals have appeared and in many instances the condition is allowed to progress to a stage where definitive surgical therapy is both difficult and hazardous, if not impossible. There appear to be many factors responsible for this state of mind, the following probably being the most important:

First, the slow progress of the disease and the relatively small number of cases which ultimately require operative therapy.

Second, advanced inflammatory changes may be present in the colon without causing proportionate signs and symptoms, so that often the physician is unaware of the stage of the disease and the imminence of complications.

Third, the fact that it is generally believed (and probably rightly so) that diverticulitis is not a forerunner of cancer. There is not sufficient awareness, however, that in the late stages it is difficult and often impossible to distinguish cancer from diverticulitis by any means.

Fourth, this attitude seems in part to be a legacy from the past when the results of operative interference were often very poor. It is only within relatively recent years that the general acceptance of defunctioning colostomy and the availability of potent antibiotics plus many other important concurrent advances in surgical knowledge have made definitive surgical therapy reasonably safe.

Fifth, the formidable nature of the operative treatment, comprising, as it most frequently does, a colostomy and multiple operations covering a period

of a minimum of six months, weighs heavily in the minds of both patient and physician

In the past, surgical treatment was not considered to be indicated unless one or more of the following complications were present severe unremitting obstruction, perforation with its secondary sequelae, or fistula formation This attitude towards surgery still persists, and consequently when many patients are finally referred to the surgeon the condition has advanced to a stage where operative cure is virtually impossible What is needed is general recognition of the excellent results of properly timed operative treatment and a clearer knowledge of the indications for operation It is not necessary at the moment to give these in detail, but speaking generally, it may be said that in the second stage of the disease, where irreversible inflammatory changes are present in the colon, if a patient should continue to suffer with moderate or severe attacks of diverticulitis *in spite of adequate palliative therapy*, then surgical treatment should be advised

There are several features of the surgical therapy of this condition which are of great interest and the subject of considerable discussion Among these are the following the place of colostomy as definitive treatment with subsequent closure without excision of the affected area, primary resection of the colon with or without complementary colostomy, the formation of a colostomy at the time of laparotomy for local or diffuse peritonitis following perforation, and the necessity or otherwise of excision of all the diverticula At this time all that can be offered in regard to these problems is that in general in this condition, because of the infective process and the possibility of poor healing, all safety factors should be observed Fixed routine methods of treatment are dangerous Each case must be decided completely upon its individual merits

As has been indicated in the foregoing, it is felt that persistence of the inert and ultra-conservative attitude of the past towards the surgical therapy of diverticulitis is responsible for much of the morbidity and mortality that still attends treatment Properly timed surgical therapy gives such comparatively excellent results that it is imperative that the profession at large gain a clearer understanding of the danger signals of impending complications and advise operative interference at an earlier stage

FREDERICK I LEWIS



SOME LIMITATIONS OF VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER

A CRITICAL FOLLOW-UP ANALYSIS OF FIFTY CASES^{*}

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INTRODUCTION

We are presenting in this report, a careful and critical follow-up analysis of 50 cases of intractable, non-obstructing duodenal and marginal ulcer treated by transthoracic vagotomy. In none of these cases was any supplemental surgical procedure performed so that changes in the course of the disease could not be referred to more than one operative factor. This is a continuing survey, the end results of which will not be complete for many years to come. However, the findings, even at this early date, have been sufficiently convincing to encourage us to publish this interim analysis.

HISTORICAL

It is not our purpose to review the voluminous literature on surgery of the vagus nerves. We have been impressed with the fact that the clinical use of vagotomy, like many other surgical procedures, occurs in cycles. In reviewing the literature it became apparent that vagotomy was utilized in the treatment of peptic ulcer over a generation ago in a number of the European clinics. Although follow-up reports are meager, it is obvious that the procedure did not live up to expectations since it virtually dropped out of the literature after 1921 until revived by Dragstedt more than 20 years later. Attempting to discover the reasons for its original clinical use and its subsequent abandonment, the early European literature was reviewed and appropriate references made thereto. In the early part of this century experimental work on animals^{1, 2} subjected to vagotomy produced conflicting observations regarding the pro-

^{*} Published with permission of the Chief Medical Director, Dept. of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author. Submitted for publication May, 1949.

duction of peptic ulcers, spasm of the pyloric sphincter, and gastric atony. Based upon the work of Foerster who resected the posterior root nerves of the D-X, XI, and XII for the pain of tabetic crises, Exner,⁶ in 1911, was the first to resect the vagus nerves in the treatment of peptic ulcers. The publication of his results was followed by trials of this operation in several of the larger clinics of Europe. Several different methods of achieving a complete division of the vagus nerves were tried, some being admittedly inadequate. On the other hand, many of the clinics are noted for the thoroughness of their work in other fields, and on this basis it must be assumed that their claim of complete division of the nerves is substantially correct. Bircher⁷ published his results in 1920 in a series of 20 cases of peptic ulcer and claimed a good result in 13 cases, fair in four, no benefit in one case, and two recurrences. He does not mention the time interval between operation and evaluation of results, nor is there any later follow-up in the literature.

After revival of the procedure by Dragstedt, vagotomy was utilized by many clinics with uniformly encouraging results as reported in the literature.⁸⁻²⁹ In these reports, the good results claimed for vagotomy must be considered in the light of short follow-up periods and the fact that a majority of cases received, at the same time, gastroenterostomy, gastric resection, pyloroplasty or some other surgical procedure which alone might be expected to influence the final result.

From the literature it is difficult to gain a clear concept of the influence of vagotomy *alone* on the clinical course of the disease process. Variations in the type of cases selected, the presence or absence of obstruction, and incompleteness of follow-up observations, are all factors which serve to obscure the issue. Certainly those cases upon whom other surgical procedures are performed concurrently, cannot be considered in any analysis which attempts to answer the question. The warning notes sounded by Lahey,³⁰ Walters^{31, 32} and Bockus,³³ have been borne out by our findings which rather strikingly fail to confirm the more optimistic observations of other workers in the field.

CLINICAL STUDY

With these thoughts in mind, the surgical staff of this hospital undertook to attempt an answer to the problem in August, 1946. It was felt desirable to determine the long term effect of vagotomy alone upon the clinical course of selected patients with duodenal or marginal ulcer. Accordingly, certain criteria were established in order to select as homogeneous a group as possible. Further to insure uniformity, each case was presented before operation to the entire surgical staff and no case was selected for vagotomy unless it met the following criteria:

- 1 Symptoms of intractable pain, chronic bleeding, or both
- 2 Failure to control symptoms by adequate medical regimen
- 3 Evidence of active ulcer by roentgen ray
- 4 No retention, clinically or by roentgen ray

Patients with gastric ulcer or with acute hemorrhage were not considered suitable candidates for vagotomy. Since the study began in August, 1946, 54 cases have been subjected to vagotomy with one death,—a mortality rate of 1.9 per cent. Of these 54, only 50 are reported in this series. The two most recent cases have not been observed sufficiently long to permit evaluation of results. One case of duodenal ulcer with obstruction was treated by gastroenterostomy and subdiaphragmatic vagotomy. Another patient received a cardioesophagostomy for achalasia of the esophagus. Because of a concurrent intractable duodenal ulcer, vagotomy was performed at the same time. Although good results have been observed in both of these cases after one year, they are not included in the series because of the uncertainty of ascribing the results to the vagotomy or to the associated surgical procedure.

The remaining 50 cases, on which this report is based, include 41 patients with duodenal ulcer and nine with marginal gastrojejunal ulcerations. Patients were all of the male sex with ages ranging from 21 to 58 years with an average of 37 years, 44 were white and six colored. The duration of symptoms varied from four months to 30 years, with an average of six years. All cases had intractable ulcer pain, and 64 per cent, in addition, gave a history of one or more episodes of gastro-intestinal bleeding. All 50 cases were operated upon through the lower left transthoracic route, with or without rib resection. In each case the vagus nerve trunks were isolated, transected, and a segment of nerve removed for histologic verification.

Postoperatively an indwelling Levine tube was kept under constant suction for three days, after which the patient was placed on a liquid diet. Persistent atony was treated by continuous gastric suction, parenteral feedings, and urecholine (Carbaminoyl-Beta Methylcholine Chloride), 5 to 10 mg three times daily.

While in the hospital patients received a standardized preoperative work-up which included histamine gastric analyses, overnight secretion studies, insulin (Hollander) tests and gastro-intestinal roentgenograms. These were repeated in the early postoperative course and again upon readmission for follow-up examination.

IMMEDIATE POST-OPERATIVE RESULTS

Symptoms In all except two cases there was complete or nearly complete relief of ulcer pain. In a number of cases it was difficult to evaluate this immediate effect because of the predominance of symptoms of gastric atonia.

Gastric Secretion Twelve-hour overnight secretion which averaged 970 cc was reduced to 290 cc in the early postoperative period. Maximum free hydrochloric acid values in the overnight specimen dropped from an average of 44 units preoperatively to 23 units postoperatively. Insulin hypoglycemia tests were performed pre- and postoperatively according to the method described by Hollander³⁴. Where postoperative responses were equivocal, the test was repeated one or more times. In the early postoperative period Hol-

lander tests showed a negative response in 82 per cent, indicating adequate section of the vagus nerves. In 6 per cent the test was not performed because of severe symptoms of obstruction which promptly developed. One of these patients was the single postoperative death encountered. The second developed such severe obstruction that he required gastric resection three weeks after vagotomy. In the third case the patient was uncooperative and left the hospital. In two cases (4 per cent) the insulin response was equivocal and in four cases (8 per cent) was positive. Of these last six cases (12 per cent) in which complete vagus section was not demonstrated, results were "good" in four (8 per cent), "fair" in one (2 per cent) and "failure" in one (2 per cent). As will be seen, the end results in this small group do not differ in pattern from the remainder of the cases in which complete vagotomy was demonstrated.

Complications. Pleural effusion was diagnosed in 40 per cent of the cases postoperatively and probably occurred to some extent in an even greater number. This complication was not of great moment and subsided in all cases either spontaneously or after thoracentesis. Two cases (4 per cent) developed atelectasis and pneumonitis. One case (2 per cent) developed a wound infection and one case (2 per cent) acute pericarditis with effusion which cleared spontaneously.

By far the most troublesome complications developed as a result of disturbances in gastric motility. Fullness in the epigastrium, belching, pyrosis, regurgitation and vomiting were noted in varying degrees of severity in 80 per cent of the cases early in the postoperative course. This was associated with loss of stomach tone, gastric enlargement, diminished peristalsis, retained gastric contents and delay in emptying time. Barium studies to determine functional changes of the stomach revealed normal motility in only 40 per cent of the cases in the postoperative period. Ten per cent showed mild gastric dilatation, 40 per cent showed moderate enlargement of the stomach or six hour gastric retention, or both, 20 per cent showed enlargement over twice the normal size or more than 50 per cent gastric retention after six hours, or both.

Five patients (10 per cent) developed early in the postoperative period such severe and unrelenting atony that further surgery was necessary. Gastric resection was performed in four of these five cases from three to 15 weeks postoperatively after strenuous efforts by the use of gastric suction and urecholine had failed. The fifth case was in such poor condition from pre-existent hepatic disease that only gastroenterostomy was performed. This failed to halt the patient's downhill course and he died three months and 20 days following vagotomy.

FOLLOW-UP STUDIES

Few reports in the literature indicate the method of securing follow-up data. It is presumed that questionnaire responses supplied much if not all of the information in the majority of cases. We have been impressed with the serious limitations of this method of evaluating symptomatic results granting

that it may, at times, be the only practical means of securing information. Personal interview associated with careful laboratory and roentgen ray studies form, in our opinion, a method of evaluation least likely to result in interpretative error.

For such reasons all patients in this series were requested to reenter the hospital for a brief period while necessary studies could be accomplished. Only three cases (6 per cent) were not subsequently hospitalized. Two cases (4 per cent) had admissions to other hospitals from which information was received. All other cases (90 per cent) have been readmitted to this hospital from one to four times for careful evaluation and laboratory examinations which included overnight secretion studies, gastric analysis, insulin (Hollander) tests, and fluoroscopic and roentgen ray studies of the gastro-intestinal tract. Excluding the five cases of early failure, follow-up has been secured in all cases extending from six months to two and a half years, an average of 18 months. One of us has personally interviewed each patient in an attempt to equalize the personal equation in the evaluation of symptomatic results. Data on all 50 cases are summarized in Table I.

Symptoms. Evaluation of symptomatic results was based on the presence or absence of postoperative ulcer pain and/or bleeding, or of the secondary effects of denervation, and the patient's estimate of his condition as compared with his preoperative status. The following definitions are given for the assigned adjective rating:

Excellent	No symptoms of ulcer or atonia
Good	Some ulcer symptoms, but definitely ameliorated, or slight to moderate symptoms of atony,—or both
Fair	Return of ulcer symptoms or severe atony or both, but condition better than preoperative state
Failure	Return of ulcer symptoms at least to preoperative severity,—or severe atony requiring further surgery, or both

Results are summarized in Figure 1. Failures are divided arbitrarily into "early" and "late,"—all five (10 per cent) of the "early" failures required further surgery within three and a half months of vagotomy—because of persistent atony with obstructive symptoms. "Late" failures (24 per cent) had initial relief followed by recurrence of symptoms from three to 24 months (average 10) postoperatively. Three of this group came to gastric resection and one to gastroenterostomy from six to 27 months after vagotomy.

Out of the 17 failures, "early" and "late," nine cases came to further definitive ulcer surgery. One case (No. 22) was the single postoperative death in the series. It is noteworthy that three cases (Nos. 14, 17, 31) later developed marginal ulcers, two following gastric resection and one following gastroenterostomy.

Pain. Although initial relief of ulcer pain was noted in 80 per cent of the cases, return or persistence of characteristic postprandial ulcer distress was

TABLE I (Continued)

X Ray Findings																			
Case No	Age	Race	Type of Ulcer	Symptoms P = Pain B = Bleeding	Duration years	Insulin test post-operative (Hollander)			Early Postoperative (< 3 mos)			Follow-Up (> 3 mos)			Follow Up Symptoms (*Early Failure)			Remarks	
						+	-	+	+	-	+	-	+	-	+	-	+		-
							+	-	+	-	+	-	+	-	+	-	+	-	
31	56	W	D	PB	30	-	A	1	3 1/2	1	1	15	+	+	+	+	+	+	Gastric resection at 3 1/2 mos for unrelenting atony Marginal ulcer 5 mos later
32	24	W	D	PB	4	-	2	2	9	3	3	15	+	+	+	+	+	+	Mild ulcer pain No bleeding Mild symptoms of atony
33	21	W	D	P	4	-	A	2	15	1	2	14	+	+	+	+	+	+	Pain recurred after 13 mos Moderate atony severe atony
34	42	W	D	PB	5	-	2	2	14	1	2	14	+	+	+	+	+	+	Pain recurred after 10 mos No bleeding Moderate atony
35	52	W	D	PB	15	-	A	1	-	1	1	14	O	+	+	+	+	+	No pain or bleeding Moderate symptoms of atony
36	55	W	D	PB	7	-	A	1	7	3	1	13	O	O	O	O	O	O	Symptom free despite persistent gastric atony and retention
37	37	W	D	PB	10	-	2	2	13	3	2	13	O	+	+	+	+	+	Symptom free
38	29	C	D	P	5	-	A	1	-	-	-	2	+	+	+	+	+	+	Gastric resection at 2 mos for persistent pain and severe atony Died of pulmonary embolus, 27 days later
39	32	W	D	P	5	+	A	1	7	2	1	7	+	+	+	+	+	+	Complete relief for 3 mos followed by mild ulcer pain

VAGOTOMY IN TREATMENT OF PEPTIC ULCER

40	38	W	D	PB	6	-	1	2	12	3	2	12	O	O	Fair	Pain relieved 9 mos postoperatively
41	41	W	D	PB	14	+	1	4	6	3	4	7	+	O	Good	Complete relief for 6 mos followed by mild ulcer pain No bleeding X-ray shows spasm of afferent jejunal limb
42	28	C	M	PB	1	-	1	4	6	3	4	6	++	O	Failure	Pain recurred after 3 mos No bleeding X-ray shows spasm of afferent
43	10	W	M ²	P	3	-	1	4	6	3	4	9	+	O	Good	Complete relief for 3 mos followed by mild ulcer pain
44	46	W	M ¹	P	4	-	1	2	9	3	4	9	+	O	Good	Gastric resection at 2½ mos for persistent pain and extreme atony and retention
45	54	W	M ¹	P	15	-	1	1	-	-	-	9	+	O	Good	Symptom free despite ulcer niche and gastric retention
46	56	W	M ¹	P	3	-	1	2	11	1	2	22	O	O	Excellent	Recurrence of pain and bleeding after 9 mos, with persistent ulcer
47	33	W	M ¹	P	13	-	1	1	14	1	2	19	++	+	Failure	Pain relieved Moderate symptoms
48	16	W	M ²	P	2	U	2	3	16	3	2	16	O	+	Good	Pain recurred after 3 mos Moderate symptoms of atony
49	57	W	M ¹	PB	13	-	1	3	-	U	U	11	++	+	Failure	Mild pain No bleeding
50	51	W	M ¹	PB	3	-	1	1	9	1	2	9	+	O	Good	Partial relief of pain for 7 mos There after no pain No bleeding
51	51	W	M ¹	PB	3	-	1	1	7	1	1	13	O	+	Good	Mild symptoms of atony

1 Marginal ulcer following gastroenterostomy
 * Marginal ulcer following gastric resection
 ** 3 weeks duration of marginal ulcer Duodenal ulcer symptoms for 28 years

noted to occur to some extent in 28 cases (56 per cent) in the short follow-up period to date. Being aware of the possibility that future pension ratings might influence the veteran's complaints we attempted a correlation between symptoms and roentgen ray findings of all cases in the follow-up period as follows

No symptoms — Normal roentgen-ray findings	27 per cent
No symptoms — Positive roentgen-ray findings	20 per cent
Symptoms — Positive roentgen ray findings	27 per cent
Symptoms — Normal roentgen ray findings	13 per cent
Either factor unknown	13 per cent

Bleeding Of 32 cases complaining of bleeding preoperatively, 7 (22 per cent) noted bleeding at some time during the follow-up period. Two additional cases who had no preoperative bleeding, noted tarry stools after operation. Knowing the long interval that may occur between bleeding episodes, the fact that bleeding appeared in one-fifth of our cases even in the short follow-up period (18 mos), throws serious doubt on the alleged protective value of vagotomy against this phase of the ulcer process.

Roentgen Ray Findings Ulcer Healing—In order to determine the effect of vagotomy on healing of the ulcer, gastro-intestinal series were performed one to four times in all but six cases during the follow-up period. The results are summarized in Figure 2.

To insure uniformity 80 per cent of the fluoroscopic examinations and review of all of the roentgen ray films were performed by one roentgenologist. Criteria for activity of a duodenal ulcer were those customarily accepted by roentgenologists—namely, the demonstration of an ulcer niche or a tender, deformed bulb with irritability and/or spasm. For marginal ulcer activity the demonstration of a niche was required.

Roughly, two out of five cases in this series were noted to have active ulcers in the follow-up period. On many of these, healing had been demonstrated in the earlier postoperative months with reactivity being noted up to two years after vagotomy. More frequent roentgen rays, particularly if taken in coincidence with exacerbations of ulcer symptoms, would most likely increase the observed incidence of recurrent ulcer.

Atonia—This term is used to include the alterations in motility nearly uniformly observed fluoroscopically following parasympathetic denervation of the stomach. Characteristically they include gastric enlargement, diminution in tonus, decreased peristalsis, and retention of gastric contents. That this retention is not due to spasm of the pyloric sphincter was repeatedly demonstrated by the fluoroscopist who could manually express barium through a flaccid pylorus into the duodenum. The extreme degrees of these changes were noted early in the postoperative course. Although tonus was regained in the majority of cases, 18 (36 per cent) had definite atony with six hour gastric retention from seven to 27 months after operation. This stands in contrast to the recent findings of Ritvo, *et al*³⁵. The follow-up observations are presented in Figure 3. These roentgen ray findings coupled with additional observations on func-

tional alterations noted in the gallbladder, large bowel and kidneys will form the material for another paper

Secondary Symptoms Closely correlated with roentgenologic observations of gastric atonia are those symptoms associated directly with section of the vagus nerves. Again the early symptoms of bloating, fullness, regurgitation,

FIG 1

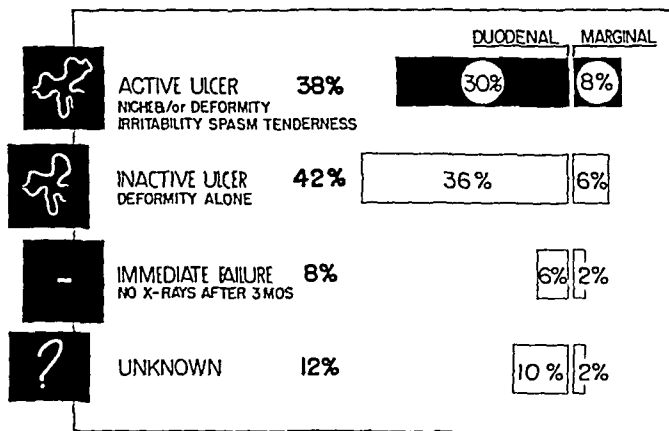
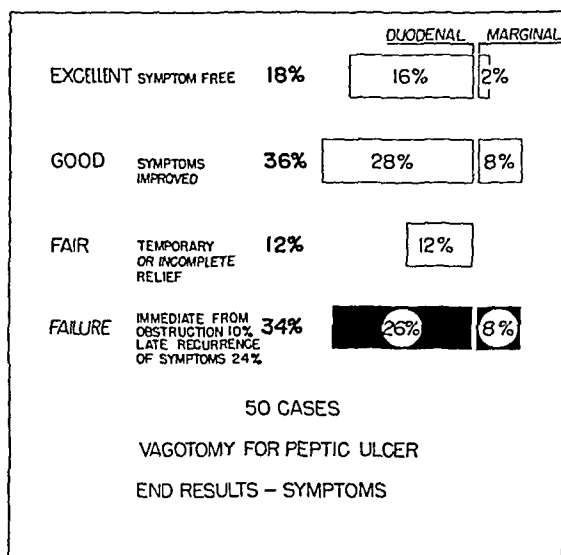


FIG 2

FIG 1—Results observed six to 30 months post-operatively

FIG 2—End results of vagotomy as determined by roentgen ray appearance of ulcer

vomiting and diarrhea either disappear or are greatly ameliorated in the majority of cases after several weeks. In contrast to some earlier reports, persistent diarrhea was not an outstanding complaint in the follow-up period, occurring in only two cases (4 per cent). Persistence of symptoms, however, is not as infrequent as previous reports have led us to believe. Excluding the early failures due to unremitting atonia, 49 per cent of cases during the follow-up period

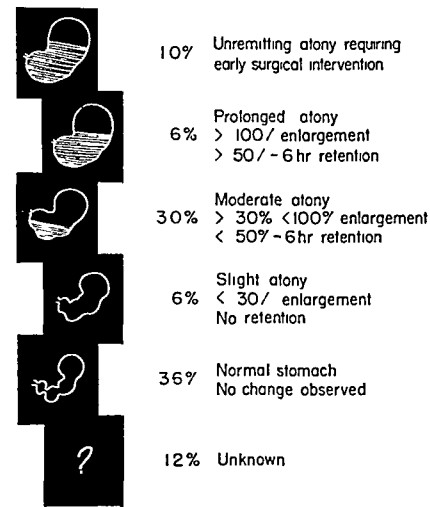
presented significant symptoms which in 9 per cent formed a source of serious disability. Considering the entire series, only 46 per cent escaped severe or prolonged symptoms attributable to nerve section.

Gastric Secretion In general, 12-hour overnight secretion volumes tended to increase during the follow-up period with values intermediate between the preoperative and early postoperative levels. Free HCl was repeatedly observed in cases which had demonstrated achlorhydria shortly after vagotomy. In at least six cases (12 per cent) insulin tests previously negative or achlorhydric became equivocal or positive, usually associated with recurrence of symptoms. We cannot explain this observation, but we doubt that it is due to regeneration of the vagus nerve fibers. Considerable difficulty was experienced in the interpretation of some results and there were many conflicting tests done only a few days apart.

CASE REPORTS

Brief protocols of all cases are contained in Table I. Pertinent observations are offered in the 17 cases classified as failures.

Case 1—A 41-year-old white male first noted hematemesis three years before admission. Roentgenograms revealed a duodenal ulcer. Subsequently he had many episodes of pain, hematemesis and tarry stools necessitating hospitalization on three occasions. At the present admission roentgen rays revealed an active duodenal ulcer with a niche. Overnight gastric secretion was 1550 cc with a free acid of 55 and a total acid of 75 units. Transthoracic vagotomy was performed on August 30, 1946, with relief of pain. Repeated postoperative insulin tests showed a negative response. He was relieved of pain for three months, after which mild symptoms were noted until two years



EFFECT OF VAGOTOMY ON GASTRIC MOTILITY
AS DEMONSTRATED BY X RAY

FIG 3—Roentgen ray observations of secondary changes following denervation.

after operation, when there was full return of preoperative pain and tarry stools. Three follow-up roentgenograms at three, seven and 14 months had demonstrated a healed ulcer, but the fourth series done two years postoperatively revealed an active ulcer with a niche (Fig 4).

Comment In this case vagotomy was followed by relief of symptoms and healing of the ulcer. The effect was temporary, however, with return to preoperative status after two years.

Case 4—A 58-year-old white male presented a four-month history of postprandial abdominal pain, hematemesis and tarry stools. Roentgenograms revealed a large duodenal ulcer crater. Acid values were within normal limits. The patient had two further hematemeses and tarry stools while under medical treatment over a period of two months. On November 20, 1946, transthoracic vagotomy was performed with relief of symptoms. Insulin test was negative. The patient was free of ulcer pain or

bleeding for 24 months. Roentgen rays at three, six and 11 months showed healing of the ulcer and a moderate degree of atony. Twenty-four months after vagotomy the patient had abdominal distress and hematemesis for which he was readmitted. Roentgen rays now revealed, (Fig 5), a large filling defect of the greater curvature of the stomach. Laparotomy was performed 27 months after vagotomy and a large tumor occupying the posterior wall of the distal half of the stomach was resected (Fig 6). Histologic examination revealed the tumor to be a reticulum cell lymphosarcoma. A portion of the resected duodenal bulb showed no evidence of ulcer.

Comment The question naturally arose whether the tumor existed at the time of vagotomy 27 months before. All films were reviewed by the entire radiology staff and it was definitely felt that the patient originally had a duodenal ulcer which healed after vagotomy. The tumor mass of the stomach could not be observed even in retrospect in the many films taken during the follow-up period. It is possible, but not likely, that the atony secondary to nerve section may have altered the radiologic criteria for detection of the earlier stages of the tumor. Certainly if transabdominal exploration had been done initially, this question would not still be unanswered.

Case 8—A 39-year-old white male gave a three-year history of ulcer pain with several tarry stools and one episode of perforation nine months before admission. Overnight secretion was 840 cc with a free acid of 80 and a total acid of 113 units. Roentgen rays revealed a duodenal ulcer with a niche. Vagotomy was performed on January 28, 1947, with relief of pain and an uncomplicated postoperative course. Insulin hypoglycemia test showed complete achlorhydria. He noted only moderate epigastric fullness and belching and remained free of ulcer symptoms for 2 years. Fourteen months after operation he developed typical symptoms and signs of acute appendicitis and appendectomy was performed.

After two years, ulcer pain returned with its preoperative severity. Although he has secured partial relief from diet and antacids, he has lost much time from work because of pain. At 25 months roentgen rays revealed a duodenal ulcer niche and the insulin hypoglycemia test was now equivocally positive.

Comment This case demonstrates the temporary effect of vagotomy on ulcer symptoms, roentgen ray findings, and the cephalic phase of gastric secretion.

Case 14—A 32-year-old white male presented a three-year history of intractable ulcer pain with hematemesis on four occasions, the last one two weeks prior to admission. Overnight gastric secretion was 875 cc with a free acid of 20 and a total acid of 50 units. Roentgenograms revealed a duodenal ulcer niche. After five weeks of medical treatment only partial relief was obtained and vagotomy was performed on April 8, 1947. Except for a pleural effusion, the postoperative course was uneventful and he was relieved of pain. Postoperative insulin hypoglycemia test demonstrated complete achlorhydria.

After 2½ symptom-free months he passed a tarry stool. Later his ulcer pain returned and he was readmitted to the hospital six months after vagotomy. At that time roentgen rays revealed some decrease in the size and activity of the ulcer. Overnight secretion was 250 cc and the insulin test was equivocal.

Sixteen months after vagotomy he was again hospitalized for severe ulcer pain which simulated a perforation. Roentgen rays revealed an increase in the size of the

ulcer niche and the insulin test was now positive. High subtotal gastrectomy was performed on August 31, 1948. Three weeks later the patient complained of burning pain in the midepigastrium. Roentgen rays (Fig 7), revealed an acute jejunal ulcer just distal to the stomal site.

Comment Vagotomy, apparently complete, failed to prevent the development of a marginal ulcer after subsequent gastric resection.

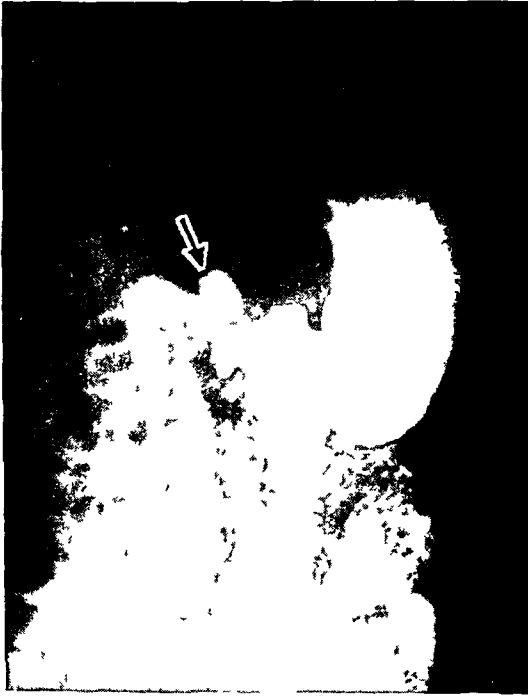


FIG 4



FIG 5

FIG 4—(Case 1) Two years after vagotomy showing active duodenal ulcer niche. Previous films had shown healing of the ulcer.

FIG 5—(Case 4) Twenty-seven months after vagotomy, roentgen ray reveals a large filling defect along the greater curvature of the stomach.

Case 17—A 29-year-old male presented a history of ulcer pain for seven years including one episode of perforation 11 months before admission. Roentgen rays revealed an active duodenal ulcer. Overnight secretion was 250 cc and acid values were normal. Transthoracic vagotomy was performed on May 28, 1947, with immediate pain relief. Insulin test was negative. Three months later he had recurrence of ulcer pain which became steadily worse and occasioned his admission to another Veterans' Hospital where, because of persistence of the ulcer and severe gastric retention, a gastroenterostomy was performed. Relief was only partial and 21 months after vagotomy he was again admitted to this hospital with his same preoperative symptoms. Roentgen rays revealed a deformed duodenal bulb. There was tenderness over the stomal site and an ulcer crater was demonstrated at the anastomosis. Insulin test was now positive. Dismantling of the gastroenterostomy and gastric resection were performed on March 30, 1949, 22 months after vagotomy. The resected specimen did not reveal a marginal ulcer despite the evidence on repeated films performed 10 days before (Fig 8). The

FIG 6

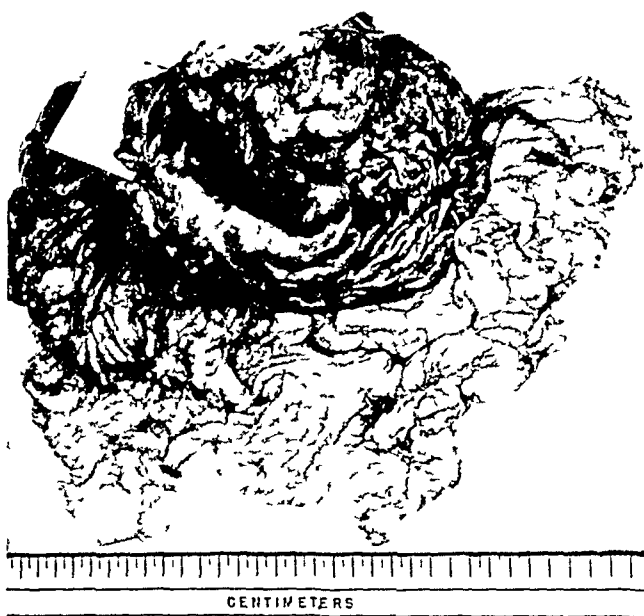


FIG 7



FIG 8

2 19 48



FIG 9

FIG 6—Resected stomach specimen (Case 4) revealing large lymphosarcoma of stomach. First portion of duodenum (on card) showed no evidence of ulcer.

FIG 7—(Case 14) Seventeen months after complete vagotomy and 22 days after gastric resection. Roentgen ray demonstrates an acute jejunal ulcer in the efferent limb of the anastomosis.

FIG 8—(Case 17) Twenty-one months after vagotomy, and 11 months after gastroenterostomy. Roentgen ray demonstrates a niche at the stomal margin. Findings observed on repeated films.

FIG 9—(Case 23) Six months after complete vagotomy. Roentgen ray demonstrates deformed duodenal bulb with a niche. Patient had relief of symptoms for four months.

Comment Because of the patient's age and chief symptoms of pain he was considered to be an ideal candidate for vagotomy. Pain relief was secured but only for 13 months, followed by reactivity of the ulcer.

Case 34—A 42-year-old white male sustained a perforation of a duodenal ulcer five years before admission. After an asymptomatic period of three years he noted ulcer pain which became increasingly severe despite medical treatment. Shortly before admission he had severe hematemesis and melena. Overnight secretion was 625 cc with a free acid of 100 and total acidity of 115 units. Roentgen rays revealed an active duodenal ulcer. Transthoracic vagotomy was performed on December 26, 1947, with relief of symptoms. Insulin test was negative postoperatively and overnight secretion was reduced to 125 cc with five units free acid and 10 units of total acid. Following discharge he noted fullness in the epigastrium and abdominal distention. After five months, roentgen rays showed an inactive ulcer and the insulin test was equivocal. After ten months the ulcer pain recurred. At 14 months roentgen rays showed an active ulcer with niche formation and 50 per cent gastric retention after four hours. The insulin test was equivocal. There has been no further bleeding and patient is being continued on a medical regime.

Comment Despite adequate vagotomy, pain recurred after ten months with reactivation of the duodenal ulcer.

Case 38—A 29-year-old colored male gave a history of duodenal ulcer pain of five years' duration. He had had several previous hospital admissions for medical treatment. Overnight secretion was 450 cc with free acid of 18 and total acid of 30 units. Roentgen rays revealed an active duodenal ulcer. On April 9, 1948, transthoracic vagotomy was performed with immediate relief of pain. Symptom relief was very transient and after several days he complained of epigastric pain, bloating and regurgitation. Roentgen rays on the eleventh postoperative day revealed a dilated atonic stomach with 75 per cent retention of barium after four hours. Overnight secretion on the sixteenth postoperative day was 270 cc with no free acid and a total of 30 units. Insulin test showed complete achlorhydria. Despite gastric suction and urecholine, the patient continued to complain of pain and lost 10 lbs in weight. On June 9, 1948, two months after vagotomy, subtotal gastrectomy was performed. Four weeks postoperatively the patient suddenly collapsed and died an hour later. Autopsy revealed a massive embolus in the right pulmonary artery.

Comment This case is not considered a fatality from vagotomy since he had fully recovered from its effects save for the gastric atony.

Case 42—A 28-year-old colored male gave a history of duodenal ulcer for five years with intractable pain and several episodes of bleeding. In October, 1947, gastric resection was performed at another hospital. He was relieved of pain for five months and then developed recurrence of pain associated with fullness, cramps, nausea, vomiting and hematemesis. Re-exploration of the abdomen was performed at another hospital in April, 1948, with lysis of intestinal adhesions. Although his obstruction was relieved, he continued to have epigastric and left upper quadrant pain partially relieved by alkalis and milk. The pain became worse and he was admitted to this hospital July 7, 1948. A G I series revealed evidence of a marginal ulcer. After an unsatisfactory trial of a careful medical regime, transthoracic vagotomy was performed on September 15, 1948. Postoperative course was uneventful and patient was relieved of pain. Insulin test postoperatively was negative. Three months later his ulcer pain recurred with only partial relief by alkalis or food. Nausea and vomiting were subsequently experi-

VAGOTOMY IN TREATMENT OF PEPTIC ULCER

enced and he sought readmission to the hospital. Marked tenderness was noted in the left epigastrium and roentgen rays revealed marked spasm of the efferent jejunal loop, although an ulcer crater could not be visualized. Insulin test was equivocal. Gastros-copy did not reveal the presence of a marginal ulcer.

Comment This case was considered a failure because of complete recurrence of preoperative symptoms and demonstrable evidence of persistent abnormality of the efferent jejunal loop.

Case 44—A 47-year-old white male had a gastroenterostomy performed for obstructive duodenal ulcer in 1939. He was relieved until 1946, when he had left upper abdominal and umbilical pain, vomiting and a 30-pound weight loss. Roentgen rays revealed narrowing of the efferent loop with two ulcer craters, and no gastric retention. Trans-thoracic vagotomy was performed on January 22, 1947. The early postoperative course was uneventful but on the tenth postoperative day there was evidence of obstruction and the patient vomited repeatedly. Roentgen rays on the thirteenth postoperative day revealed a tremendous dilatation of the stomach (Fig 11). Treatment with continuous gastric suction, prostigmine, and intravenous alimentation produced only partial relief. The patient tolerated a soft diet for two months but failed to gain weight and continued to have severe gastric atony. Insulin test revealed evidence of complete vagus nerve section. A two weeks course of urecholine (10 mg t.i.d. before meals) did not influence the obstruction favorably and on April 9, 1947, two and one-half months following vagotomy, the gastroenterostomy was dismantled, the involved jejunal segment resected and gastric resection performed. The specimen revealed a stenosis of the pylorus, narrowing of the efferent jejunal loop, and an active stomal ulcer. Six months later roentgen rays of the stomach revealed a good stoma, no ulcer and no retention.

Comment In this case an apparently complete vagotomy failed to heal a marginal jejunal ulcer after two and one-half months. The procedure apparently converted a potential stomal obstruction into a most extreme retention which was not favorably influenced by conservative therapy.

Case 46—A 56-year-old white male gave a history of painful duodenal ulcer with vomiting for 28 years. In January, 1947, a G I series revealed almost complete pyloric obstruction with deformity of the duodenal bulb. On February 4, 1947, a posterior gastroenterostomy was performed with marked relief of symptoms. He was well for four months and then developed epigastric pain with intermittent vomiting. Roentgen rays revealed a large ulcer crater just distal to the anastomatic stoma. On July 7, 1947, transthoracic vagotomy was performed with complete relief of symptoms. Insulin test was negative. Nine months postoperatively he noted left upper quadrant pain relieved by food or alkalis. Roentgen rays 14 months after vagotomy revealed a large ulcer crater in the proximal portion of the efferent jejunal loop (Fig 12). The patient has continued to have pain, with intermittent tarry stools, until the time of this report, 20 months after vagotomy.

Comment Despite apparently complete nerve section, this patient failed to gain more than five months of symptom relief and demonstrated either persistence or reactivation of the marginal ulcer.

Case 48—A 46-year-old merchant seaman gave a history of duodenal ulcer of three years' duration. Two years before admission a subtotal gastrectomy was performed at another hospital. Subsequently he underwent four laparotomies presumably for intestinal obstruction. He entered this hospital with a two-day history of severe upper abdominal pain and vomiting.

FIG 10



FIG 11



FIG 12

FIG 13

FIG 10—(Case 31) Nine months after vagotomy and $5\frac{1}{2}$ months after gastric resection for duodenal ulcer. Roentgen rays demonstrate an acute ulcer niche in the efferent limb of the jejunum.

FIG 11—(Case 44) Thirteen days after vagotomy. Roentgen ray reveals tremendous dilatation of the stomach which is filled with fluid and air and occupies two-thirds of the abdominal cavity.

FIG 12—(Case 46) Fourteen months after vagotomy for marginal ulcer. This demonstrates large persistent ulcer crater in the proximal portion of the efferent jejunal loop.

FIG 13—(Case 45) Eleven months after vagotomy for post-gastroenterostomy stomal ulcer. Despite complete symptom relief there is a persistent ulcer niche and barium retention in the stomach after four hours.

VAGOTOMY IN TREATMENT OF PEPTIC ULCER

Laparotomy with lysis of intestinal adhesions was performed on September 26, 1947. Relief was temporary and a second exploration was done nine days later with jejunio-jejunostomy to bypass an obstructed loop. The patient's pain continued and now roentgen rays revealed a large stomal ulcer crater without gastric retention. Overnight secretion was 520 cc with no free acid but 75 units of total acid. Because of persistence of pain and vomiting, and failure of previously performed laparotomies to relieve the symptoms, it was felt that the stomal ulcer was responsible.

Accordingly, on November 4, 1947, transthoracic vagotomy was performed with immediate and dramatic relief of pain. The patient became uncooperative and left the hospital before further secretion studies could be performed. Since discharge he has had recurrence of abdominal pain and persistence of the stomal ulcer.

Comment This case was not an ideal selection for vagotomy because of the difficulty of evaluating postoperative symptoms. However, the dramatic relief of pain after vagotomy, after failure of many previous operations, indicates that the stomal ulcer played a major role in the clinical picture.

SUMMARY

We have not been able to confirm the encouraging reports of other investigators with regard to the effectiveness of vagotomy in the treatment of duodenal and marginal ulcer. Fifty carefully selected cases with intractable pain, and without obstruction, were subjected to transthoracic vagotomy without any associated surgical procedure to obscure the final result. There was one death in the series. In the early postoperative period we were able to confirm previous reports with regard to nearly uniform relief of symptoms, diminution of secretory volume and acidity and a high incidence of gastric atonia.

One hundred per cent follow-up was obtained over a period of six to 30 months postoperatively, an average of 18 months. Rehospitalization was accomplished on nearly all cases from one to four times for careful symptom analysis, roentgenograms and secretion studies. Symptomatic results were excellent in 18 per cent, good in 36 per cent, fair in 12 per cent, and failure in 34 per cent. There were five failures (10 per cent) in the early postoperative period due to unrelenting atony which necessitated further surgical intervention. The remaining 24 per cent were failures because of recurrence of preoperative symptoms during the follow-up period. Roentgen ray healing of the ulcer was noted in 42 per cent of the cases but 38 per cent showed either persistence or recurrence of active ulcer during the follow-up period (three to 30 months). Roentgen ray evidence of gastric atony, enlargement and retention, previously reported as a transient phenomenon was observed in 42 per cent of the cases throughout the follow-up period.

In failure cases, the relief of pain afforded by vagotomy was temporary, lasting from three to 24 months. Nine of the 17 failures required subsequent gastric resection or gastroenterostomy. Three of these cases later developed marginal ulcers despite apparently complete nerve section. There was no evidence that vagotomy favorably influenced symptoms of bleeding which was noted in 22 per cent of cases in the follow-up period.

Although the period of follow-up observation of these cases is somewhat short to draw final conclusions, nevertheless, the relatively large percentage of unsatisfactory results noted up to the present time is very significant and clearly indicates that the procedure has serious limitations in the treatment of peptic ulcer. In reconciling the poor results noted in this series with the favorable reports of other observers it must be remembered that frequently the latter are based upon vagotomy in combination with gastroenterostomy. It is commonly recognized that gastroenterostomy alone gives generally excellent early results but that the duration of beneficial effects is inversely proportional to the length of the follow-up period. Only after observations have been made over many years will we know whether or not the combination of vagotomy with gastro-enterostomy or other surgical procedures is a rational one.

According to our data a patient who is subjected to vagotomy has one chance in five of securing complete relief, two chances in three of being benefited to some extent, and one chance in three of failure—all within an average of 18 months postoperatively. For this rather dubious benefit he must accept a small but nevertheless significant mortality risk and the unhappy prospect that his continued freedom from ulcer symptoms is by no means assured. Half the time he must also pay an additional premium in the form of persistent symptoms of gastric atony which not infrequently may be more disabling than the original ulcer.

On the whole, we feel that vagotomy, even in carefully selected cases, has not proved successful in a sufficient number of cases to justify its routine use. Despite the lower operative mortality, failures are too frequent and morbidity too serious after vagotomy to justify its replacement of other proved more effective methods of surgical treatment.

CONCLUSIONS

- 1 Careful follow-up studies are reported in 50 selected cases of non-obstructed duodenal or marginal ulcer treated by transthoracic vagotomy without other associated surgical procedures.

- 2 Failures were observed in 34 per cent of cases after an average follow-up period of 18 months.

- 3 Previous reports of other investigators concerning the long-term effects of vagotomy on symptom relief, ulcer healing, gastric secretion, and secondary symptoms have not been confirmed.

- 4 There are serious limitations of vagotomy in the treatment of duodenal and marginal ulcer.

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SOME REFLECTIONS ON SURGICAL PRINCIPLES IN TREATING CANCER OF THE COLON AND RECTUM

BASED ON AN ANALYSIS OF 70 PATIENTS*

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THE STORY OF THE surgical treatment of carcinoma of the large bowel is somewhat like a three-act drama in which the scene and action in the last act are similar to the first. To be sure, the characters and the results are quite different. Because of the almost complete revolution in the cycle, it might be of interest to review our own series of malignant lesions of the large bowel and rectum, and to examine the data and results in an effort to determine what lessons might be learned from such constant change.

Back in the "gay-nineties" when one of us (U M) first became interested in intestinal surgery, resection of the colon with an open end-to-end anastomosis was in vogue. True, not many resections had been performed, yet Billroth¹ was able to report a series of 17 cases in 1889 with a 60 per cent mortality. During residency at Touro Infirmary, in 1898 and 1899, not one elective resection of the colon or rectum was observed. In 1903, Mickulicz² reported 24 cases in the Boston Medical and Surgical Journal with a mortality of only 16.6 per cent, having utilized a multiple-stage exteriorization procedure developed by Block³ on the continent and Paul⁴ of Liverpool. As a result of these publications most surgeons adopted staged operations as the procedure of choice for malignant lesions in all levels of the colon except the rectum.

The first successful extirpation of the rectum had been performed by Lisfranc⁵ in 1826. He used the perineal approach, which Allingham⁶ was one of the first to modify, by leaving the external sphincter in situ. Because of tension it was rarely possible to attach the remaining rectum to this muscle, and the wounds healed poorly. Despite the fact that such operations were considered "barbarism" and part of the surgery of a by-gone age,"⁷ many fine surgeons attacked the problem with vigor. In an epochal paper, Kraske⁸ advised removal of a portion of the sacrum. This was the first effort towards a more radical approach. At first Kraske was content to suture only the anterior walls of the remaining rectum, but later advised a complete anastomosis. If enough slack could be attained, Hochenegg⁹ pulled the proximal portion down to the anal skin or, if this was impossible, he created a sacral anus.

Because of technical difficulties, Czerny,¹⁰ in 1883, was compelled to do a combined abdomino-perineal resection. Later, Maunsell¹¹ and Quenu¹² advocated the combined method as an elective procedure. Fifty years ago, Tuttle¹³ stated, in words which sound as if they might have been written yesterday,

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"Where the tumor is limited to that portion of the intestinal tract entirely surrounded by peritoneum abdominal resection is undoubtedly superior to all others and can be quickly executed by [aseptic methods] Where the tumor is well below the promontory of the sacrum, however, in that portion of the gut only partially covered by peritoneum, complete removal by this route alone is attended with many difficulties" Mann,¹⁴ of Buffalo, advocated anterior resection and anastomosis for all lesions of the rectum proximal to the distal two inches in an article published in 1901, the same year that he tried to save the assassinated McKinley

Miles,¹⁵ in 1908, presented reasons for the radical removal of lower sigmoid, rectum and anus which were so convincing that the debate of anterior resection versus posterior resection was almost silenced Babcock¹⁶ and Bacon,¹⁷ however, have continued to fight for preservation of the sphincters and perineal anus, and Horsley¹⁸ and Dixon¹⁹ for anterior resection

In 1928, Rankin²⁰ modified the exteriorization operation with the introduction of obstructive resection accomplished by a special clamp Several years later he reported 31 cases with a mortality of 3 per cent²¹ In the meantime proponents of a one-stage operation, because of the extremely high incidence of infection, experimented with various closed methods of anastomosis to achieve asepsis O'Hara²² and Schoemaker²³ devised special clamps, Martel,²⁴ an ingenious steel bow, and Parker and Kerr²⁵ the basting stitch In 1940, Kerr²⁶ stated that over 40 methods of aseptic anastomosis had been described Improved clamps devised by Furniss,²⁷ Stone²⁸ and Wangenstein,²⁹ among others, have given further impetus to the closed method There is unquestionably a decided trend, at the present time, towards the more frequent use of aseptic primary anastomosis (Gibbon³⁰) Nevertheless, a number of eminent authorities still prefer extraperitoneal obstructive resection, particularly in the distal colon, as they have found that they obtain a lower mortality with two sittings

A further debatable point has been the use of proximal decompression Wilkie,³¹ Whipple,³² Cheever,³³ Dixon,³⁴ and others favored proximal cecostomy or colostomy Stone and McLanahan,³⁵ Wangenstein,³⁶ and Waugh³⁷ are among those who oppose it in the non-obstructed case

The introduction of intestinal chemotherapy by Firor and Jonas³⁸ has added further sub-divisions to the various camps of adherents of one or another method Finally, Meyer³⁹ has recently endorsed one-stage open anastomosis just as did Reybard⁴⁰ and Kohler,⁴¹ who started colon resection for cancer, and the stage is set just about where it was 50 years ago when the senior author first started his surgical career

Thus, we now have those who advocate staged procedures, as well as advocates of a one-stage operation, those who believe in open anastomosis and those who prefer a closed one, those who use complementary decompression, and those who do not One school is intent on preservation of the perineal anus, either by "pull-through" operations or anterior resection, while another

will have nothing to do with such conservatism. And there is the group of surgeons who prefer one of the above plans but do not use preoperative chemotherapy, and the group who do. Certainly such division of opinion is confusing to the younger surgeon and makes it extremely difficult for him to select the optimum plan for his patient.

While it is obvious that no one method is best for all cases, we are convinced that adherence to certain fundamental principles will enable the surgeon to choose the method best suited to the majority of his patients. First and foremost is earlier diagnosis and surgical intervention, Second, is radical extirpation of the lesion and its lymphatic pathways, Third, is adequate physiologic and pharmacologic preparation of the patient, Fourth, is complementary proximal decompression to avoid distention and tension on the suture line, Fifth, is simplicity and adaptability of technic.

These fundamentals are reviewed in the light of our experience with 70 consecutive operations on the colon and rectum done during the past 16 years, all from the surgical service at Touro Infirmary.

1 *Earlier Diagnosis* The rise in resectability rate and lowering of operative mortality leave little to be gained by advances in technic or management alone. The only hope for an improvement in curability lies in extending diagnostic measures. Consequently, we must adopt the obvious principle of earlier recognition as the corner-stone of any group of rules.

Since many of the symptoms given in many texts are of little actual value in making an early diagnosis, attention must be directed towards earlier abnormalities of function. These include recurrent bouts of vague abdominal distress, darkening in color or specks of blood in or on the stools, and gradually changing bowel habits. In these days of oil and radio-ballyhooed "nature remedies," constipation often passes unnoticed, but the use of steadily increasing amounts of laxatives by a patient may be a valuable lead. With such hints a complete physical examination is indicated. This must include sigmoidoscopy and roentgen ray studies. It should be remembered that few *rectal* lesions can be visualized by roentgenogram, but approximately 70 per cent of rectal cancers can be felt with the examining finger while almost 75 per cent of all large bowel cancers can be seen with the sigmoidoscope. Periodic physical examination in the absence of a suggestive history does not seem to be a practical approach. Given an early diagnosis, the percentage of patients with initial signs of obstruction and, thus, higher operative mortality and lessened curability, will be decreased. In addition, the number of cases with extension through the serosa, distal lymphatic metastases, and blood vessel spread will be minimized.

2 *Radical Operation* One of the major objections to exteriorization procedures is the inability to resect widely the areas of lymphatic drainage at the root of the mesentery. The danger of local implants was largely abolished by Rankin's modification. Nevertheless, multiple procedures entail multiple risks, a higher incidence of complications, and prolonged hospitalization.

The investigations of Jamieson and Dobson⁴² on lymphatic spread have been extended by Dukes and Gabriel,⁴³ Gilchrist and David,⁴⁴ and Collier and his workers⁴⁵. The number of nodes involved were found to be much greater than previously suspected. Retrograde extension occurred rarely, but blood vessel invasion was found in about 15 per cent of cases. Might it not be that the higher curability rate for right sided lesions is related to the radical hemicolectomy performed, in contradistinction to the more limited resections on the left side?

Consideration of blood supply has been emphasized by Steward and Rankin,⁴⁶ and Singleton.⁴⁷ Inconstancy in vascular anastomoses between the terminal branches of both superior and inferior mesenteric arteries must be understood by the surgeon, as viability of remaining bowel must not be jeopardized by any weak links in collateral blood supply. On the other hand, the critical point of Sudek has been de-emphasized. Observation of small vessel pulsation, reflex muscle contractility and color of the bowel will guide us in estimating adequacy of circulation. Utilizing these aids, a radical operation with immediate anastomosis is feasible.

3 *Adequate Preparation* Proper cleansing of the bowel and elimination of distention have been emphasized for many years. Advances in physiology and pharmacology have enabled us much more adequately to prepare the patient. Replacement of protein and weight loss, fluid and vitamin deficiencies, and diminished blood volume are recent advances which have added considerably to lowering of the mortality. Improvements in anesthesia and management of shock are further contributions to the procedure itself. The use of whole blood to restore a normal blood volume is of utmost importance.

Another significant benefaction, in our opinion, is the employment of intestinal chemotherapy to minimize infection. Because of well intentioned aims to emphasize other prominent factors, some surgeons have belittled this outstanding advance and others have even declined to use such drugs, but they appear to be a minority. The improvement in our mortality figures since the addition of this measure is noteworthy, and the results of numerous clinical and laboratory experiments only serve to emphasize the value of chemoprophylaxis in the preparation of the patient.

4 *Complemental Decompression* This principle has received much attention and, recently, Graham⁴⁸ has found that approximately 30 per cent of a selected group of surgeons questioned continue to use it. We readily admit that this is one of the least important measures in the non-obstructed patient, and much of its value has been obviated by tube decompression. However, we still prefer to use such a safety valve, mainly to eliminate pressure on the suture line. There is also added comfort to the patient when peristalsis proximal to the resected area begins, and the artificial vent allows elimination of gaseous distention. We have rarely had complications arising from employment of this measure which was so strongly advocated by C. H. Mayo.

5 *Technic* It should be emphasized that we must be open-minded in the selection of the particular type of operation indicated in the individual

patient Of course, earlier diagnosis means earlier operation, thus avoiding those conditions which may invalidate primary resection with immediate anastomosis Our success will depend on operation before obstruction, perforation or gross infection have occurred, all of which may require proximal drainage or deviation of fecal stream before any definitive surgery can be attempted

If a definitive procedure is feasible, we believe that the simplest and most direct one which allows achievement of the aforementioned principles will give the best results Hence, a one-stage resection with end-to-end anastomosis is advocated Because closed types of anastomosis entail additional steps, we

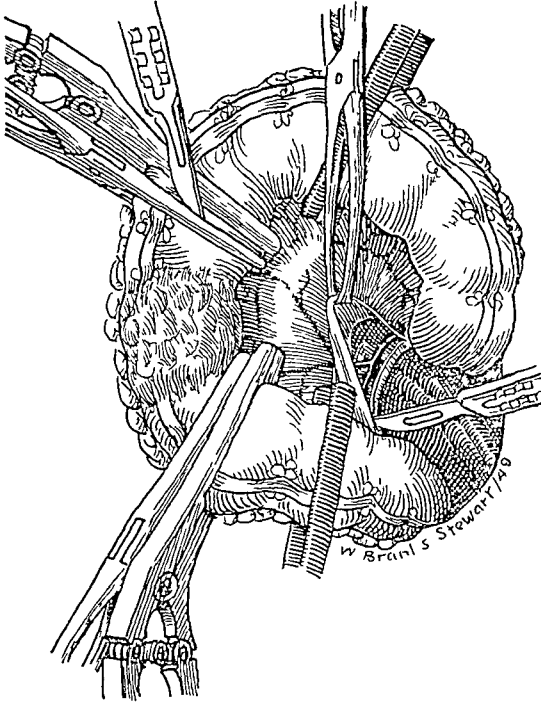


FIG 1

FIG 1—Excision of bowel between Payr clamps Mobilization by incising avascular "Monk's white-line"



FIG 2

FIG 2—"U"-shaped resection of mesentery rather than usual "V" Angulation towards anti-mesenteric border as described by Madelung

prefer open anastomosis The preoperative use of a non-absorbable sulfonamide makes this procedure relatively safe

Some of the more significant technical details of a sigmoid resection are discussed The abdomen is entered through a left rectus-splitting incision with the patient in slight Trendelenburg position Spinal anesthesia is preferred Exploration is done and, unless there is evidence of widespread metastasis, resection is attempted The peritoneum is incised at its reflection from the mesentery (Monk's white line) (Fig 1) After the major vessels are visualized they are clamped, cut and ligated If the lesion is a low-lying one, steady

traction on the pelvic colon at this stage frequently gives added exposure. The mesentery of the bowel is then cut, not in the usual "V" manner, but in a broad "U," to and including its root, thereby enabling the maximum of lymph bearing tissue to be removed (Fig. 2).

Rubber-shod clamps are placed on the near and far sides of the tumor to interrupt any fecal flow. As much bowel as possible on both sides of the lesion

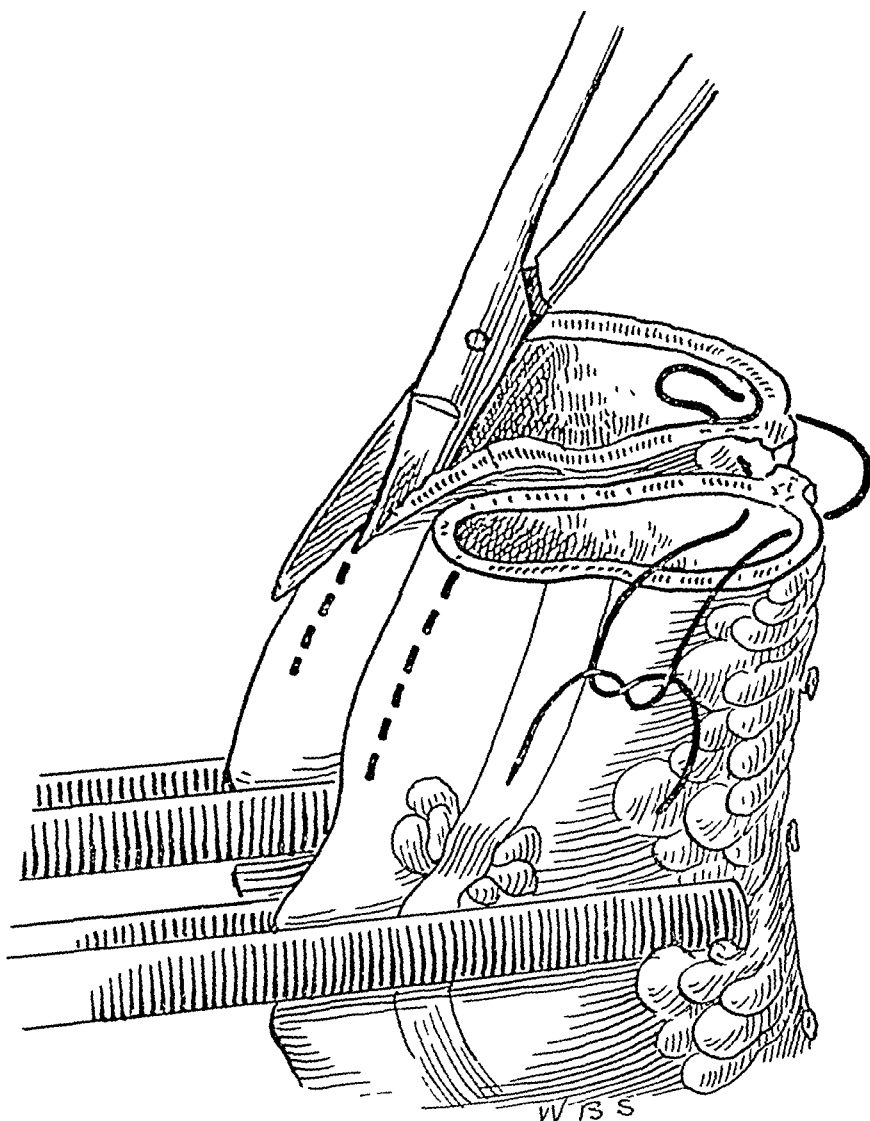


FIG. 3—Utilization of Cheatle's slit on anti-mesenteric border to increase and equalize lumen

is sacrificed, consideration being given to the fact that the two ends must be brought together without tension. With Allis clamps marking the site of resection, thin-bladed Payr clamps are placed at an angle of approximately 60° to the mesenteric border, as initially suggested by Madelung⁴⁹. The actual portion to be excised is clamped with Kocher forceps and the colon severed with a sharp knife. We do not like the actual cautery. Heating clamps with the cautery may be responsible for transmission of excess heat to adjacent bowel with subsequent slough. We do appease surgical sensibilities by wiping

the open ends with an iodine sponge. The Payr clamps are removed and the crushed tissue trimmed off. The viability of these margins is then checked, and if there is doubt as to adequate blood supply more bowel must be resected.

Because of the inequality in the diameter of the two ends of the intestine,

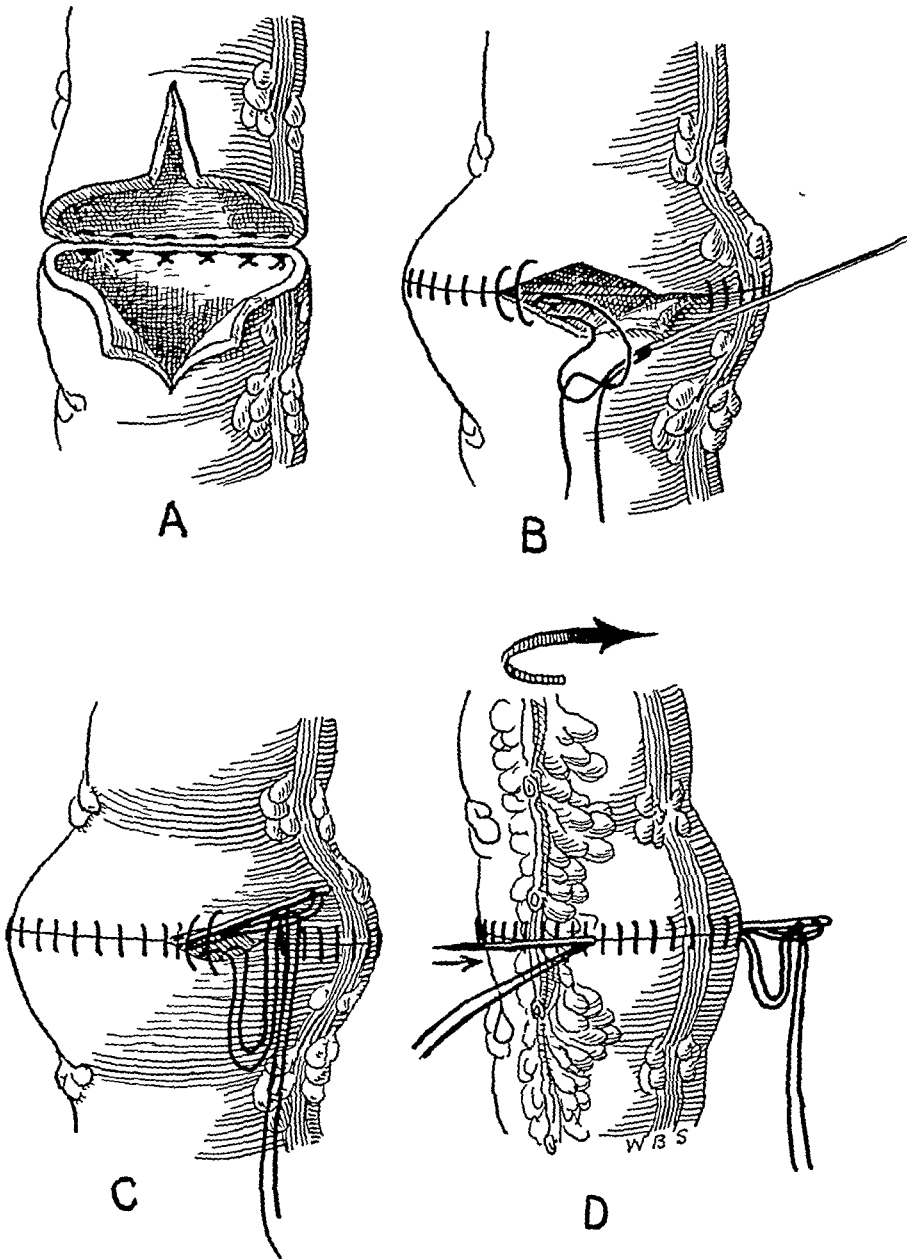


FIG 4—A and B Progressive steps in the placement of Connell's suture
C and D The only new feature of this suture as stated by Connell was the method, as shown here, of securing the final suture so that all knots are on the inside

the smaller end or both are usually split for a varying distance on the anti-mesenteric border, described first by Cheatele⁵⁰ (Fig 3). End-to-end anastomosis is then accomplished by means of a single layer of interrupted Connell⁵¹

"U" sutures with all knots tied in the lumen (Fig 4) Fine silk is used on a straight intestinal needle If placed carefully and with attention to detail, one row of sutures provides a perfectly adequate hemostatic and water-tight closure (Fig 5) For added precaution the ends of adjacent appendices epiploicae are

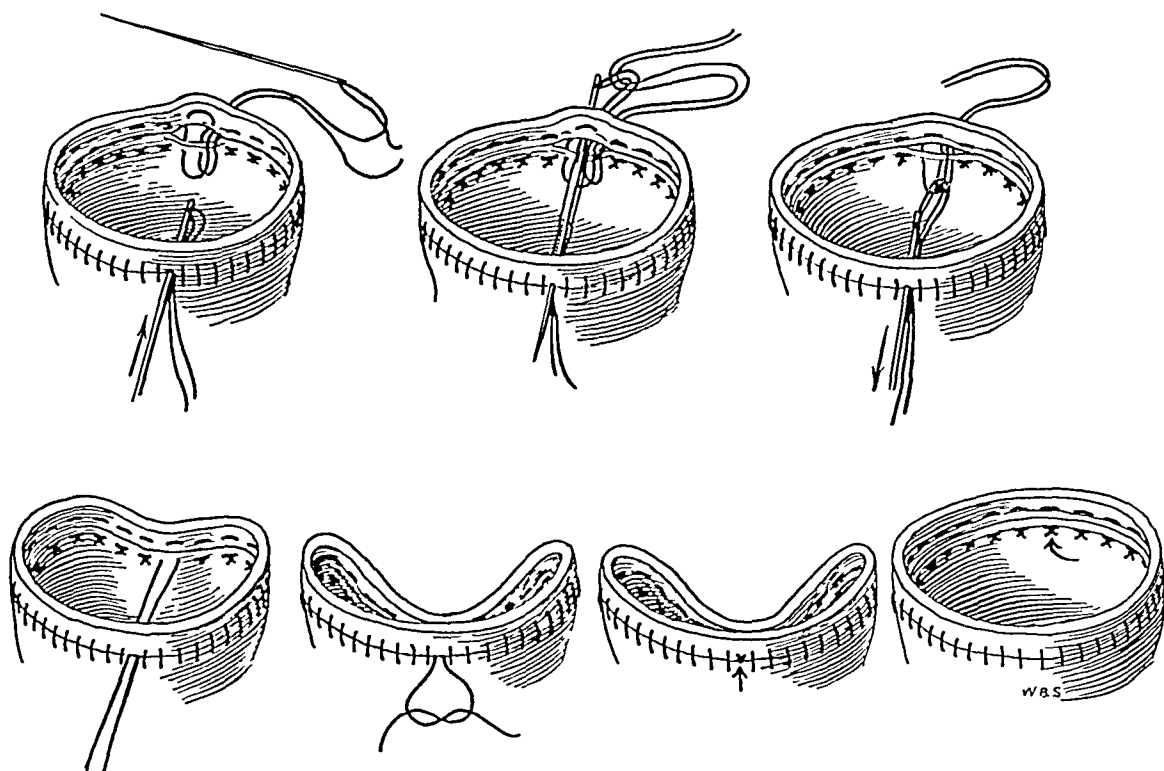


FIG 5—Diagrammatic sequence of securing last suture so that knot though tied and cut on outside remains in interior

tacked over the suture line One row of sutures obviously produces less diaphragm than several rows (Fig 6) Single-layer closure has been used in 26 consecutive cases (including three colotomies for removal of malignant polyps) during the past eight years without an operative death

Reperitonealization is accomplished, after which a Stamm-type colostomy using a Pezzar catheter is done several inches proximal to the suture line The end of the catheter is passed through an

opening made in the omentum and out the upper margin of the incision, or sometimes through a small stab wound in the flank to humor the residents

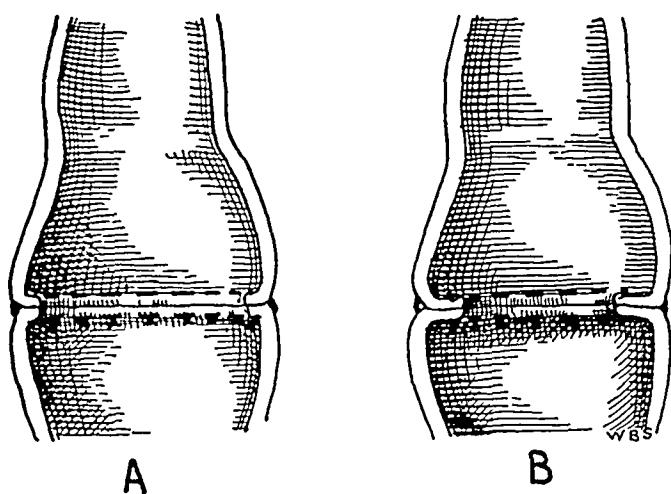


FIG 6—A Result attained by use of one row of sutures

B Formation of partial diaphragm with use of additional suture layers

The suture line is then inspected and sulfanilamide crystals sprinkled over the area. The omentum is replaced and the wound closed in layers.

If there has been no excessive weight loss and the abdominal wall appears strong, the peritoneum is closed with continuous catgut, and the fascia with interrupted silk. But if the various layers seem to be unduly pale or attenuated, or there is a history of marked wasting, the peritoneum and fascia are closed as a single layer employing Whipple's⁵² far-and-near figure-of-eight stitch. Formerly, silk was used for this suture, but because of the large bites of tissue taken, we now use medium chromic catgut. If the fatty layer is very thick, Babcock wire-retention sutures through the fascia are emplaced and fastened with Davey buttons. No drains are used. If there has been unexpected spillage, the peritoneum alone is closed and the remainder of the wound packed with dry gauze.⁵³ Secondary closure can usually be performed four to five days later and, at that time, the fascia and skin may be closed with interrupted sutures.

Postoperative Measures. Five hundred cubic centimeters of blood is usually given during the procedure and, postoperatively, as indicated. Penicillin is routinely given for four to five days. Fluids are given sparingly by mouth the first day, and all liquids, except milk, freely on the second day. Sufficient intravenous fluids are given to insure a urinary output of 1000 to 1500 c.c., depending on the patient's age and cardio-renal status. Less saline has been given in recent years although we have always preferred to keep our patients slightly more on the "dry" than on the "wet" side. If it is necessary to check the salt balance of the patient, the urinary chloride output can be accurately and easily estimated, as emphasized by Marriott.⁵⁴

The patient is encouraged to sit up early. Frequent changes in position, leg exercises, and stimulation of deep breathing with 10 per cent carbon dioxide are useful in the postoperative period. There seems to be a tendency on the part of many present-day surgeons to overtreat his patients. We prefer to treat complications as, and if, they arise, and for that reason do not advocate such extreme measures as prophylactic femoral vein ligation, and so forth. The revival of simplicity in surgery is a welcome sign.⁵⁵

Extent of Operation. A right hemi-colectomy is now the standard procedure for lesions of the right half of the colon. Wide resection with end-to-end anastomosis is, likewise, generally accepted for the transverse colon. The splenic flexure offers special problems.⁵⁶ In addition to being a greater diagnostic problem, its high and fixed position may present technical difficulties. Obstruction is not uncommon, and a proximal decompression of some type may be necessary.

For the left side of the colon, the closer the lesion approaches the peritoneal reflection, or "clinical recto-sigmoid junction," the more vigorous the debate becomes as to the proper operation. As a result of the centrifugal lymphatic drainage described by Miles and Lockhart-Mummery, the older school of surgeons used a higher dividing line to make the choice between local resection

and the more radical abdomino-perineal operation The more recent studies have all emphasized the predominant upward spread from the rectosigmoid and most of the rectum Nevertheless, these same investigators (Gabriel,⁵⁷ Rankin,⁵⁸ David⁵⁹) still strongly advocate the principles propounded by Miles

It is our opinion that the peritoneal reflection is the lowermost limit for abdominal resection in the majority of cases, and for lesions below this line we prefer the combined operation Nevertheless, the trend at present is un-

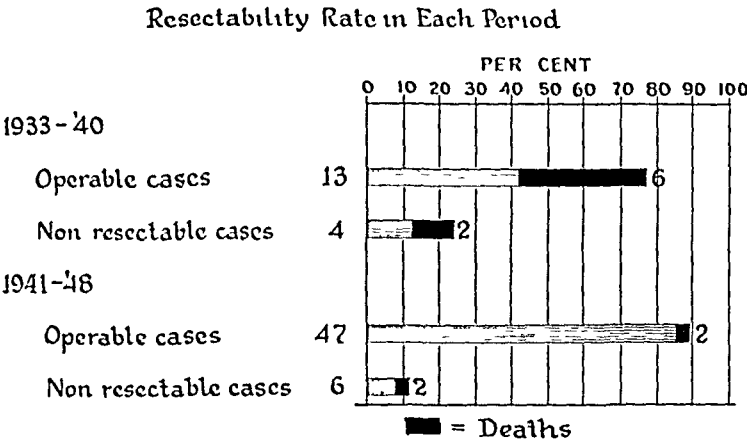


FIG 7—Graphic representation of improvement in resectability and mortality in the two eight-year periods

TABLE I—Types of Operations Performed in 70 Consecutive Cases

		1933 – 1941		1941 – 1948	
		Cases	Deaths	Cases	Deaths
Rectal Cases 25					
Abdomino-perineal	16	3	1	13	1
Post resection	6	1	0	5	1
Removal of polyp	1	0	0	1	0
Non resectable	2				
Colon Cases 45					
Primary E E anast	29	6	3	23	0
2 stage Mikulicz	5	3	2	2	1
Colotomy (polyp)	3	0	0	3	0
Non resectable	8				

doubtedly toward anterior resection for lesions extending down into the upper portion of the rectum, and the results obtained by Dixon,⁶⁰ Wangensteen,³⁸ Best⁶¹ and others must be given careful attention

While posterior resection, with excision of coccyx and part of sacrum, is done on occasion, we believe its use is strictly limited to a small group of aged and feeble patients who do not appear able to withstand a more formidable operation, or who show evidence of distant metastases

Analysis of Cases A new era began in 1941 with the introduction of intestinal antibiotics The lead of Firor and Jonas was quickly followed up on our service, and the various sulfonamides have been used ever since For this

reason, we have divided this series of cases in two groups from 1941 to 1949, and a comparable eight-year period prior to 1941 (Fig 7 and Table I). The earlier group includes 17 cases, 13 of which were resected. There were eight deaths or a mortality of 47 per cent. We were able to obtain autopsies on all of these, and it was found that six of the deaths were due to peritonitis, one resulted from pulmonary embolism and one from a perforated duodenal ulcer. There are 53 patients in the more recent period, of whom 47 were resectable. There were two deaths in this group, or a mortality of 4.2 per cent. Two of the six non-resectable cases died. One of the patients died after four months from generalized carcinomatosis, and another in one month from a pulmonary embolus, one from shock and anuria, and only one from peritonitis. This last patient was admitted with acute obstruction and, on exploration, a perforation was found. There is a decided reduction in mortality in the latter group. Undoubtedly, a number of factors are responsible, but we agree with Pemberton⁶² that the major one is the assistance given by chemotherapy.

The resectability rate in the earlier period was 75 per cent as compared to 89 per cent in the later one. The mortality is understandably much higher in the non-resectable cases—50 per cent in the first group and 33 per cent in the second. These patients all had acute intestinal obstruction on admission and required immediate operative decompression. Nothing further could be accomplished for them.

There is nothing remarkable in the age or sex incidence. There are more females than males—and women also predominate in the younger age groups. Most of the patients were in the sixth decade. The average age of the males was 64 years and of the females, 61.5 years. Three patients were in their eighties and, fortunately, all three survived resection.

Almost three-fourths of the large bowel lesions were located in the sigmoid colon, and the remainder equally divided between the ascending and transverse colon. There were 25 rectal lesions, which is a lower percentage than usual (Fig 8). The concentration of colon and rectum tumors in the recto-sigmoid region is cogent reason for the continuing debate on the optimum approach to such lesions.

Six patients had malignant polyps, two of which were associated with carcinomas of the sigmoid colon. One patient had multiple polyposis with malignant transformation. There was one double malignancy of the rectum and colon with neoplastic infiltration of a complicating ileo-colic fistula. A block resection of colon and ileum, end-to-end anastomosis of ileum, and abdomino-perineal resection was done on this 70-year-old man and, when checked recently, he was well and working.

DISCUSSION

It has been said that if cancer of the bowel started like a toothache we could expect many cures. Unfortunately, malignancies of the intestinal tract have no hall-marks for early diagnosis. Being suspicious of minor signs or symptoms

should make for earlier recognition before metastasis has occurred. Thus, more patients will be seen who are not yet the victims of anemia, toxemia, partial obstruction or the other complications which contribute to the discouraging chapter on cancer of the colon and rectum.

Large series of studies have shown that one-third to one-half of all malignant lesions of the large bowel and rectum are within reach of the finger (70 per cent of rectal cancers). About three-fourths of all such malignancies are within reach of a 10 in proctoscope. A finger or look in the rectum gives more information, frequently, than a thermometer in the mouth.

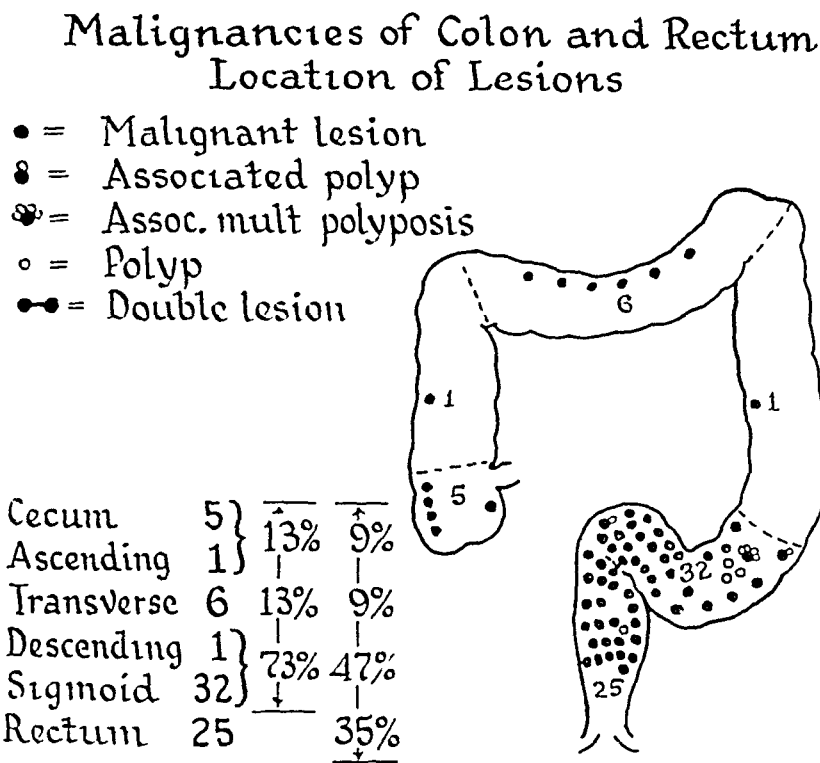


FIG. 8.—Distribution of lesions. Note that most occur in region of recto-sigmoid.

It is well to recall that the operation of Miles was the turning point in the successful management of cancer of the gastro-intestinal tract, and it was only after his publications that we began to think in terms of curability. Before 1907 recurrences were well over 90 per cent. Only the early low neoplasms offered any hope at all. With improvements in technic, more thorough preparation of the patient, chemoprophylaxis, blood transfusions and improved anesthesia, the operative mortality has been reduced to safer limits with a five-year curability of 50 per cent or more. An important point in lowering the operative mortality of the combined procedure, in our opinion, was recognition of the fact that it is not necessary to turn the patient on his face for the perineal dissection.

It is obvious that wide resection with restoration of the lumen is the operation of choice in the right half of the colon as well as the transverse colon.

This holds true for the left colon down to the distal sigmoid. The closer the lesion approaches the peritoneal reflection, the greater the controversy becomes as to the indications for the Miles procedure in its entirety, or whether a local resection with immediate anastomosis does not serve an adequate purpose. The permanent colostomy is still the main objection offered by patients to the radical operation. If, however, the patient can be convinced that he has a better chance of living with a colostomy than with an incompletely removed cancer, he will naturally choose the colostomy.

We believe that it is necessary to weigh many factors in making this decision. Some patients are extremely poor candidates for any type of artificial anus, because of age, feebleness, lack of aid, mental make-up, and so forth. This group should be eliminated for consideration of colostomy, if possible. It must be realized that high (sacral) implantation of the rectum is no more satisfactory than an abdominal colostomy. The so-called "posterior resection with preservation of sphincter control" has been unsatisfactory, in that a good anastomosis is not often possible, and slow healing due to poor blood supply and infection is common. Some of the more recently suggested "pull-through" operations may be successful so far as recovery is concerned, but unless the lesion is very early and limited to the upper half of the rectum, the disruption of rectoanal reflexes diminishes sphincteric continence to the point where it is of little practical value (Gaston⁶³), and such operations cannot be recommended.

We may have been influenced in the past by the statements of the pathologists that the lymphatic spread was "upward, outward and downward." By studying those patients who have had recurrences, as well as the recent investigations on lymphatic drainage, we are forced to wonder about downward spread. Consequently, for sigmoid lesions down to the peritoneal reflection we feel that anterior resection is justified. In the group of patients previously mentioned, anterior resection might be extended to lesions located a few inches below the peritoneal reflection if complementary proximal colostomy is done. According to Gray,⁶⁴ a patient's chances for cure, with a lesion of the recto-sigmoid, is diminished by no more than 3 per cent if the abdominal approach alone is used, perhaps not at all (Kirklin⁶⁵).

For all other lesions of the rectum, it seems to us, the glands heading toward the aortic chain and along the levators should be the principal ones for attack. With these in mind it seems logical to conclude that the Miles operation or its modifications offer a better chance of cure than will less extensive excision with restoration of continuity.

The decision as to open or closed anastomosis is not too difficult to make. Whichever is easier for the operator to perform well should be selected, so long as his mortality rate remains in the neighborhood of 5 per cent. This relatively low rate is being achieved by more and more surgeons using either method. As emphasized by Rives,⁶⁶ it is more the manner of execution that counts rather than the method. If the morbidity and mortality can be further reduced appreciably by staged operations, then this plan, of course, should be

adopted Otherwise, it seems that the advantages of primary resection and anastomosis far outweigh those of multiple procedures, except in the complicated case

The use of complemental decompression can also be gauged by comparative morbidity and mortality studies There is no question that long tube decompression, as well as increased knowledge of the physiology of peristalsis, have lessened the advantages of operative decompression However, unless its disadvantages become more obvious we shall continue to use this measure

The results obtained in carcinoma of the colon and rectum have kept general pace with the advances in surgical technic and knowledge Nevertheless, we must not allow ourselves to become self-satisfied or complacent The last word in treatment of patients with intestinal cancer is far from written, as witness the fact that many abandoned or maligned procedures find new applications with increased knowledge It is doubtful whether any really new procedure can be devised We should study diligently the lessons of the past and correlate them with present advances in the all-out effort to achieve further improvements for the unfortunate cancer victim

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THE USES OF PLASTIC TUBES IN THE REPARATIVE SURGERY OF BATTLE INJURIES TO ARTERIES WITH AND WITHOUT INTRA-ARTERIAL HEPARIN ADMINISTRATION*

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BACKGROUND

DEBAKEY AND SIMEONE in an excellent review article¹ point out that 68.6 per cent of over 3000 amputations performed in two theaters of operation in World War II were necessitated by tissue loss alone, 19.5 per cent were due to arterial injuries *per se*, and 11.9 per cent were caused by gas gangrene and other infections. They indicate that the tremendous amount of tissue destruction caused by the speed and multiplicity of modern war missiles and the time lag between injury and treatment decide the fate of the majority of limbs before reparative surgery can be undertaken. It is possible, however, that in the event of another war the increasing number of civilian casualties from air raids may reduce this interval between injury and treatment. Furthermore, the enormous tissue destruction and loss of collateral circulation show clearly that the only hope for avoiding gangrene with these injuries lies in maintaining patency of the main artery to the limb—at least until post-traumatic edema subsides and collateral circulation becomes re-established.

The best methods for repairing these arteries are unfortunately impractical under battle conditions. The suture technics of Carrel and Guthrie will not bridge the gaps left by the loss of arterial substance. The technic of Blakemore² using venous-lined vitallium tubes preserves the principle of intima-to-intima coaptation, but is usually too time-consuming and complex for use under battle conditions by the average military surgeon. A simple reparative technic using lucite tubes was introduced toward the end of the last war. The method was not properly evaluated because of the unfavorable conditions during battle for making follow up observations and controlling the important variables. This investigation was undertaken to determine how well plastic tubes bridge gaps in arteries and the reasons for their relative success or failure. The ideal reparative technic for arteries ablated in battle should be simple, avoid thrombosis effectively, and use materials well tolerated in tissues.

Lucite, a methyl methacrylate polymer, has been shown to be relatively well tolerated in animal and human tissues. Polyethylene,† another synthetic plastic, is made by polymerizing ethylene under heat and pressure to hydro-

* The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large. Submitted for publication January, 1949.

† The polyethylene tubing used in these studies was of formulation PHF, purchased from Surprenant Mfg. Co., 199 Washington Street, Boston, Mass.

carbon chains somewhat longer than those of paraffin. In addition to its chemical similarity to paraffin, polyethylene has the advantage of being flexible without plasticizers and in this respect is more suitable for replacing segments of arteries near joints.

TABLE I—*The Coagulation Time (Minutes) of Blood in Contact with Various Surfaces*

Series	Poly-ethylene	Lucite	Glass	Paraffin	Collodion	No of Comparisons	End Point	Diam of Tubes (mm)	Blood Used
Authors	11.5	—	5.3	12.4	12.5	30	Earliest sign of clotting	5	Canine
Hirschboeck	—	13.9	6.2	18.3	—	10	Complete clotting	10	Human

Ingraham, *et al*³ have reported that pure polyethylene caused minimal foreign body reaction and gliosis when implanted in the cerebral cortex of animals. They stressed the importance of using pure polyethylene, however, because any traces of the antioxidants or plasticizers used commercially to enhance its insulating or flexible properties have incited marked fibrosis and foreign body reaction. To establish the purity of the polyethylene used and to study its reaction in tissues, small pieces of polyethylene and lucite were inserted subcutaneously in the backs of 30 rats at the outset of this study. The animals were sacrificed at intervals postoperatively and the tissues surrounding the plastic studied histologically. Figure 1 shows that the tissue reaction at three months to pure polyethylene resembles that caused by the relatively well-tolerated lucite.

✓ Clotting times were then performed under controlled conditions in glass and polyethylene tubes and in glass tubes lined with paraffin and collodion. The *in vitro* capacity of polyethylene for delaying coagulation is similar to that of lucite (Table I), being about twice that of glass and nearly as great as paraffin and collodion.⁴ Surface tension studies (Table II) indicate that

TABLE II—*The Values (Gm/cm) for the Adhesive Force Between Water and the Surfaces of Polyethylene and Glass. These Figures Are Compared with Hirschboeck's Values for Glass, Lucite, Paraffin and Collodion⁵ and the Established Value for Glass⁶*

Series	Polyethylene	Lucite	Glass	Paraffin	Collodion
Authors	+0.034	—	+0.073	—	—
Hirschboeck	—	+0.038	+0.053	-0.037	+0.034 ⁷
Harkins and Brown	—	—	+0.0736	—	—

polyethylene, like lucite, follows Lampert's rule that the capacity of a surface for delaying coagulation is inversely proportional to its "wettability."^{1,7}

With this background polyethylene tubes were first tested by bridging gaps in the aorta of dogs with a technic similar to that of Hufnagel, who reported permanent anastomosis of the thoracic aorta of dogs using lucite tubes.⁸

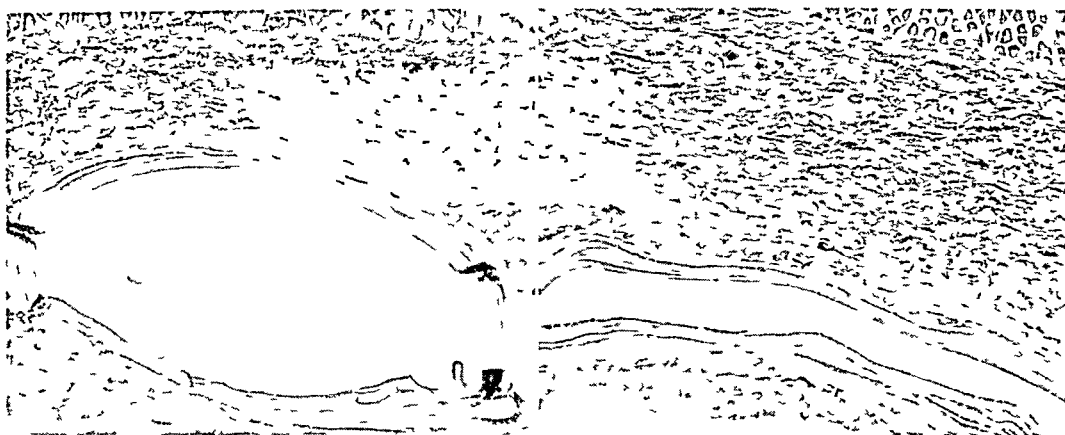


FIG 1

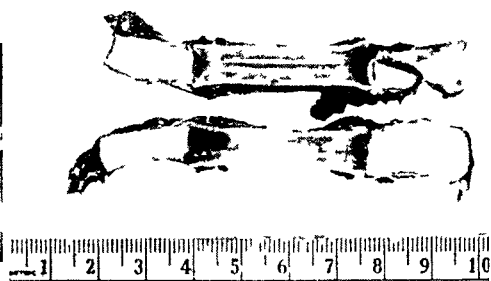
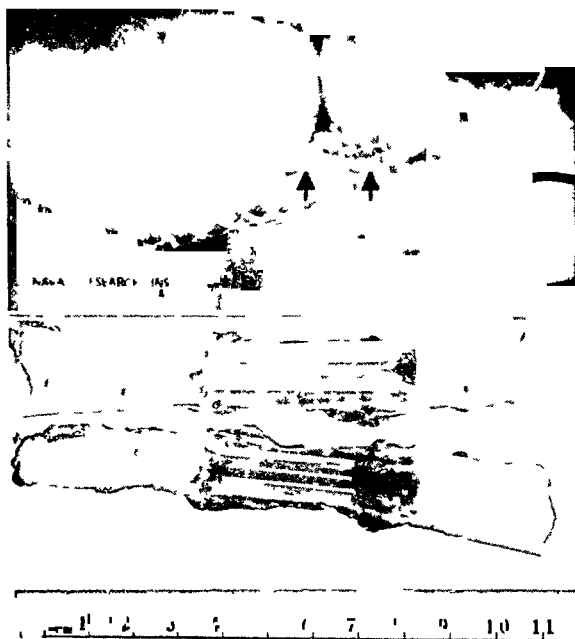


FIG 3

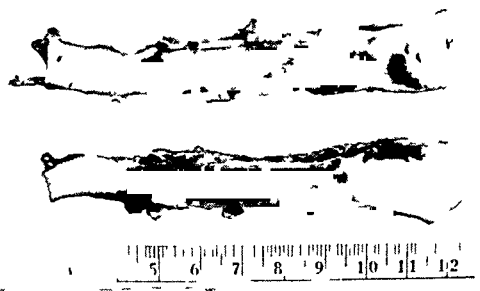


FIG 5

FIG 1—The tissue reaction to polyethylene (A) and lucite (B) three months after subcutaneous insertion into rats. The fibrous capsule surrounds the space from which the plastics were removed during fixation. The width of each piece of plastic represented by the diameter of the capsule was about 2 mm while the length approximated 1 cm.

FIG 2—Roentgen ray of the thoracic aorta 12 months after anastomosis with a polyethylene tube of 5 mm i.d. Arrows indicate the ends of the tube.

FIG 3—The aorta and tube of the animal in Figure 2, showing the tissue proliferation bridging over the vulnerable tube-vessel junction, thus inhibiting thrombosis.

FIG 4—An aorta and tube partially thrombosed nine months postoperatively.

FIG 5—A completely thrombosed aortic intubation in a dog sacrificed six months postoperatively. Both ends of the clot are almost completely covered with endothelium.

I. AORTIC INTUBATIONS

MATERIALS AND METHODS

Description of the polyethylene tubes Stock polyethylene tubing of 5.5 and 7.5 mm i.d. was divided into lengths of 4 to 4.5 cm and turned to a wall thickness of about 1 mm. The internal diameters were chosen to stimulate the size of the human femoral artery. Holding ridges of 1 mm width and height were left about 5 mm from each end of the tube. The ends of the tube were turned almost to knife-edge thinness and then flared by slowly inserting a smooth metal die heated to the softening temperature of the polyethylene. If any flaw was found on any part of the tube, it was discarded. The tubes were ✓ sterilized in 70 per cent alcohol or 1 to 1000 zephiran for 18 hours prior to operation.

Operative technic The animals were premedicated with 0.25 grain of morphine, 0.01 grain of atropine and anesthetized with 6 per cent nembutal (1 cc per 5 pounds body weight). Supplementary doses of nembutal were given later as needed through a plastic tube introduced into the vein of the front leg after the method of Zimmermann.⁹ Positive pressure oxygen was given during the operation through an intratracheal tube of Koroseal by a mechanical respirator.

The seventh rib was resected and the pleural cavity entered through its bed. Five pairs of intercostal arteries were ligated and divided to make patency of the anastomosis more critical to the animal's survival. Division of these intercostal arteries probably eliminated the intercostal-to-intercostal collateral routes and impeded the subscapular-intercostal and internal mammary-intercostal anastomoses. It did not, however, interfere with the internal mammary-inferior epigastric pathways of collateral circulation. The aorta was then freed from the thoracic duct and vagus nerve and the Gross aortic clamps applied for hemostasis.¹⁰ The aorta was then divided or a short segment excised and the Hufnagel aorta spreader introduced distally to facilitate the atraumatic insertion of the polyethylene tube.¹¹ The limited excision was done in this study in an effort to reduce the strain on the ligatures and avoid subsequent aortic rupture from this cause. The tube was ligated in place with large braids of No. 2 silk strands, as suggested by Hufnagel,⁸ to give multiple point fixation of the aortic wall and prevent its necrosis and rupture. The ligature behind the holding ridge was applied tightly while the one nearest the flare was tied more lightly. The tube and vessel were irrigated with saline and the proximal end inserted and ligated in a similar manner. The distal clamp was then removed and the proximal clamp released gradually while the animal was placed in a moderate Trendelenburg position. This obviated the hypotensive effect of splanchnic pooling so that usually only slight tachycardia was noted on release of the clamps.¹² The period of aortic occlusion rarely exceeded ten minutes and no paraplegia from this cause occurred. The aorta was repleuralized and the chest closed with chromic pericostal and interrupted cotton sutures.

Penicillin in saline solution (500 units/cc) was used to irrigate the pleura periodically during the operation and penicillin in oil was given intramuscularly for several days postoperatively. No heparin or other anticoagulants were given at any time to these animals.

Postoperative observations The anastomoses were studied postoperatively by observations on the oscillations,* strength, and warmth of the hind quarters. Absence of paraplegia is good evidence of patency during the immediate postoperative period. Later in the postoperative course the development of collateral circulation makes this a less reliable sign. At about three months postoperatively, roentgenograms of the aorta were taken using thorotrast or 70 per cent diodrast intravenously and repeated just prior to sacrifice from 6 to 12 months postoperatively, when pathologic studies were made.

RESULTS

A Initial group In the initial group of 14 aortic anastomoses, six dogs died on an average of ten days postoperatively from aortic rupture associated with clotting in the polyethylene tube. In four of the six aortic ruptures the tubes were too large, causing intimal trauma at the time of insertion and subsequent pressure necrosis of the aortic wall. Three animals developed thrombosis and paraplegia and were sacrificed. Some of the thromboses in this initial group were due to intimal damage during insertion and/or roughness and asymmetry of the tube. The anastomoses in two animals, one weighing 9 Kg with a tube of 5.5 mm i.d. and a 21 Kg dog with a tube of 7.5 mm i.d., remained open permanently. These animals were sacrificed 12 and nine months postoperatively.

B Second series Table III shows the results of a series of anastomoses with tubes of 7.5 mm i.d. without the above-mentioned technical flaws. Two of the nine anastomoses remained permanently functional. Three of the fatalities were from hemorrhage and three from mesenteric embolism, two of the latter following large doses of intravenous thorotrast. The average length of survival in the fatal anastomoses was 51 days.

Pleural adhesions of varying density were found in all the animals autopsied more than three months postoperatively. Repleuralization of the tube and aorta did not completely prevent the adherence of pleura to the tube and adjacent tissues. The ends of the aorta, separated by the tube, were united in a few weeks by a neomembrane composed largely of fibrous tissue completely enveloping the tube. The chromic pericostal sutures and the intrapleural penicillin could not be incriminated in the fibrotic reaction, since the

* Oscillometry was recorded as 4 plus, maximal, 3 plus, moderate, 2 plus, decreased, 1 plus, minimal, and 0, absent. From 2 to 4 plus is considered normal range while 1 plus or 0 usually means decreased blood flow to the limb from thrombosis, embolism, or other causes. Oscillometric studies are valuable as corroborative data when trends and not individual observations are considered, but they do not compare with angiography for accuracy and amount of information given.

animals autopsied up to three weeks postoperatively were free of adhesions and widespread inflammatory reactions. In none of these animals was there any evidence of pleural sepsis.

C Permanent intubations Of the four permanent intubations, one was completely free of clots, two were partially thrombosed and one was completely thrombosed. Figure 2 shows a roentgenogram of the completely patent anastomosis 12 months postoperatively. Oscillations remained normal throughout the postoperative course. Figure 3 shows the appearance of the tube and aorta at the time of sacrifice. The tissue proliferation (connective tissue lined with endothelium) characteristic of the permanent intubations can be seen at both ends of the tube bridging over the vulnerable tube-vessel junctions, thus inhibiting thrombosis.

TABLE III—Results of Anastomoses of the Thoracic Aorta in Dogs with Polyethylene Tubes

No	Weight in Kg	Time of Survival	Cause of Death	Condition of Tube	Comment
1	18	8 months	Sacrificed	Small clot in tube	Roentgen ray showed patency
2	18	18 days	Mesenteric embolism	Partial thrombosis at distal tube vessel junction	
3	18	3 months	Mesenteric embolism	Small clots at tube vessel junctions	Oscillations disappeared after 40 cc thorotrast and returned after embolus
4	16	4 hours	Massive hemothorax	Fibrin deposition in tube and at proximal tube vessel junction	
5	21	4 months	Mesenteric embolism	Partial thrombosis at proximal tube vessel junction	Embolism followed 40 cc thorotrast and recurred
6	21	11 days	Aortic aneurysm with leakage	Small clots at tube vessel junctions	
7	21	4 days	Thrombosis of tube	Complete thrombosis of proximal end of tube	
8	19	6 months	Sacrificed	Complete thrombosis of long duration	Marked collateral circulation by roentgen ray
9	21	4 months	Massive hemothorax	Complete thrombosis of recent origin	Aortic rupture high above tube, marked cardiac hypertrophy

The two permanent intubations with small intraluminal clots had one to two plus oscillations during most of their postoperative course. The tubes in the aortograms were less clearly defined, also indicating partial thrombosis. Figure 4 shows one of these partially thrombosed tubes at autopsy.

Roentgen ray studies of the animal with complete thrombosis of the tube showed the complete blockage and marked dilatation of the collateral channels. The internal mammary arteries, greatly enlarged and tortuous, anastomosed with equally large inferior epigastric arteries, but no notching of the ribs was apparent. The subscapular arteries were also moderately expanded, but the lowermost intercostals were not visible. Oscillations were moderate the first month in this animal, slight during the second month and absent there-

after despite normal function of the hind legs Figure 5 shows this tube and aorta at the time of sacrifice

COMMENT

Hufnagel's five permanent anastomoses of the aorta with lucite tubes in a series of 15 intubations were notable for the complete absence of clot formation Nine of the ten fatal intubations were also free of clots⁸ These results contrast sharply with the prevalence of clotting in this study of polyethylene and suggest that lucite tubes are superior to those of polyethylene in respect to the avoidance of thrombosis The larger sizes of the lucite tubes and aortas, however, must be considered as contributing to the superior results The significance of this size factor will be discussed in the next section dealing with intubations of the femoral artery

II INTUBATIONS OF THE FEMORAL ARTERY

MATERIALS AND METHODS

Description of the polyethylene tubes Polyethylene tubing of 2.7 mm i.d. and 3.5 mm o.d. was cut into lengths of 2 to 2.3 cm The ends were flared with a hot die Holding ridges were placed around the tubes by applying melted polyethylene about 3 mm from each end of the tube Some of these tubes were soaked in heparin (sodium heparin, Lederle, 10 mg per cc) for one month before operation This was done because surface tension studies with polyethylene tubing indicated that the polyethylene absorbed water over a period of days and therefore might absorb aqueous heparin⁴ Other tubes were lined with silicone film,* which inhibits blood coagulation, by filling their lumina with silicone and silicone diluted with toluene to concentrations of 1/100 and 1/200 The toluene was baked off and the tubes rinsed for several hours in distilled water

Description of the lucite tubes Lucite tubes, 2 to 2.3 cm long, were turned from stock tubing of 3 mm i.d. with ridges about 3 mm from each end The ends were flared with a warm die, making them similar in shape to the polyethylene tubes but slightly larger in internal diameter At no time was the inner surface of the tubes scratched or handled roughly All tubes were carefully inspected for flaws and discarded if any irregularity or asymmetry was found

Operative technique The femoral artery was exposed from just below the groin to just above the knee The long saphenous artery, which arises medially from the femoral artery about 5 cm below the inguinal ligament, was freed and its branches divided A polyethylene side tube about 60 cm long, 1 mm o.d. and 0.4 mm i.d., was threaded into the long saphenous artery for about 1 cm and held in place with four cotton ligatures The other end of this tube

* The silicone was General Electric's Dri Film 9987 usually used on glass surfaces The silicone for plastic surfaces was not available

was led with a long flexible needle subcutaneously and dorsally through the skin of the costovertebral area, a location inaccessible to the animal's teeth. Through this tube 35 per cent diodrast was injected at 24-hour intervals postoperatively and the distal femoral artery visualized by arteriography (Fig 6). A stylet was placed in the end of the tube between injections to prevent retrograde bleeding and clotting in this side tube.

The branches of the femoral artery were ligated and divided from above this long saphenous artery to the bifurcation of the femoral into anterior tibial and popliteal arteries. Bull dog clamps were applied, the femoral artery divided, and the adventitia retracted from the cut ends of the vessel. After the ends of the artery were irrigated with saline the plastic tube was inserted, using a new instrument designed to retract the arterial walls. The tube was



FIG 6—A polyethylene tube bridging a gap in the femoral artery of a dog two days postoperatively. Arrows mark the ends of the tube (note increased capacity) and X, indicates the small polyethylene side tube in a branch of the femoral artery proximal to the anastomosis.

ligated in place with No. 20 cotton ligatures on each side of the holding ridges and the adventitia replaced over the ends of the tube.

The instrument used to retract the vessel walls was constructed by attaching semicircular steel rockers to the tips of an outside caliper by means of a steel pivot (Fig 7). Four barbless hooks were connected by silk suture material to the ends of the rockers. By adjusting the screwlock on the caliper, vessels of various sizes could be spread in the form of a square larger than their internal diameter (Fig 7). This instrument has facilitated the insertion of these artificial tubes and minimized intimal damage during insertion, thus obviating subsequent thrombosis from this cause.¹³

In two animals with otherwise identical technique the ends of the divided artery were ligated. In one animal circular ligatures were used and in the other the Poppen type of suture ligature was employed, which invaginates the arterial wall and apposes the intima.¹⁴

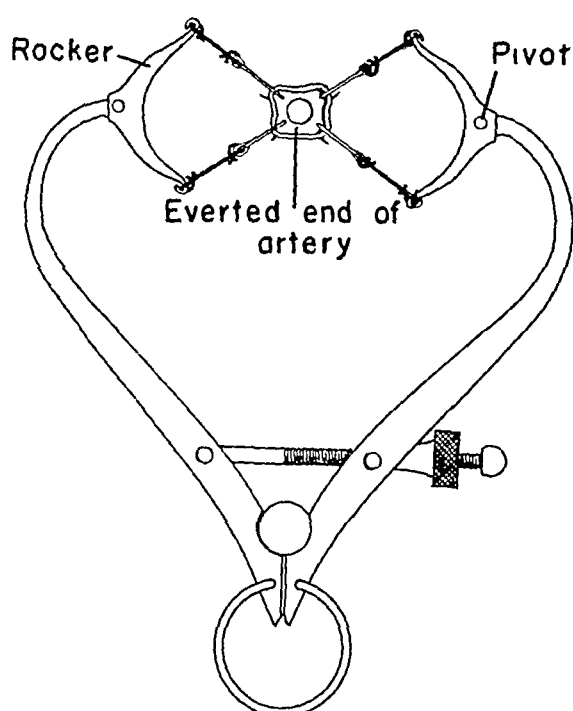


FIG 7—Diagram showing vessel spreader. Lower portion represents a four-inch caliper with screw-lock and spring. At the upper ends are the rockers attached with steel pivots. Four silk threads are shown leading to the hooks which retract the vessel walls.

Intima coaptation technics were also studied, *e.g.*, suture anastomosis and polyethylene tubes lined with veins after the method of Blakemore, *et al*² (Fig 8).

Postoperative observations. These anastomoses were studied postoperatively by daily arteriograms as described previously. In addition, observations on the oscillations, strength, and warmth of the extremities were made three times daily and the artery examined under anesthesia just prior to sacrifice.

RESULTS

A Anastomoses with plastic tubes

Duration of patency. Table IV shows a summary of the results in typical series of polyethylene and lucite intubations of the femoral

TABLE IV—Results of Anastomoses of Femoral Arteries of Dogs with Polyethylene and Lucite Tubes

Dog No	Weight in Kg	Artery	Tube	Roentgen Ray Study of Course in Hours		Duration of Patency in Days
				Patent	Thrombosed	
1	28	Right	Polyethylene	48	72	2
		Left	Polyethylene	48	60	2
2	29	Right	Polyethylene	48	72	2
		Left	Polyethylene	72	80	3
3	23	Right	Polyethylene	10	24	½
		Left	Polyethylene	10	24	½
4	33	Right	Polyethylene	48	72	2
		Left	Polyethylene	48	72	2
Average						Average
	28					1 8
1	42	Right	Lucite	96	Dog sacrificed*	4
		Left	Lucite	24	48	1
2	35	Right	Lucite	72	96	3
		Left	Lucite	120	Dog sacrificed*	5
3	28	Right	Lucite	96	120	4
		Left	Lucite	48	72	2
4	35	Right	Lucite	72	96	3
		Left	Lucite	72	96	3
Average						Average
	35					13

* Dogs sacrificed to establish patency as leakage from side tube prevented roentgen ray visualization.

artery Six out of eight anastomoses with polyethylene tubes were open on the second day on roentgen ray study with an average duration of patency of slightly less than two days The lucite tubes showed an average duration of patency of slightly over three days with six out of eight intubations open on the third day The average period of patency of the six anastomoses using silicone-lined tubes or the four heparin-soaked tubes was not longer than with the untreated polyethylene tubes Figure 6 shows a polyethylene tube in dog No 4 on the second postoperative day

Clot formation Figures 9, 10 and 11 show the development of collateral circulation following thrombosis of the lucite tubes in dog No 7 These

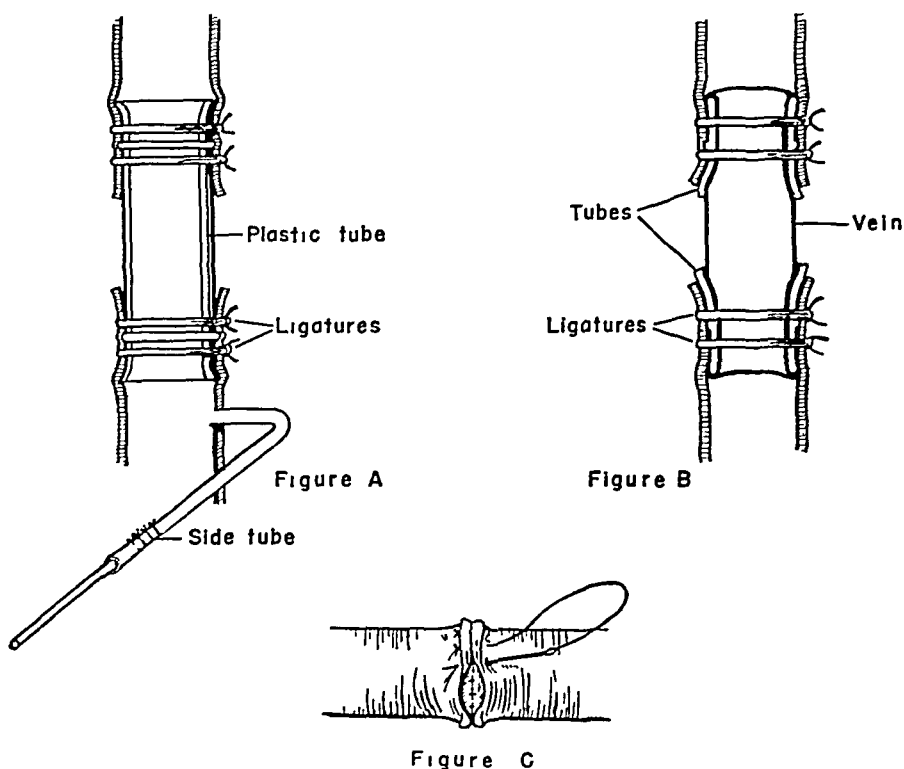


FIG 8—Three techniques for reconstructing vessels A Plastic tube anastomosis Note polyethylene side tube in a branch of the femoral artery B Venous-lined tubes, reproduced from Blakemore² C Suture anastomosis redrawn from Gross and Hufnagel¹⁰

roentgen ray films are typical of others showing the same process occurring with polyethylene intubations Following thrombosis the oscillations dropped to 1 plus or zero, but the hind legs never felt significantly cooler than the front legs Emboli were seen in several roentgenograms, partially or wholly blocking the flow in the femoral, anterior tibial, or popliteal arteries (Fig 9) In some instances their origin could be traced to the tube anastomosis by serial films No appreciable difference was noted in the process of clot formation and extension or the development of collateral circulation in these siliconed, heparin-soaked and untreated polyethylene tubes

Reaction to the lucite and polyethylene tubes The adjacent tissues adhered

FIG 9

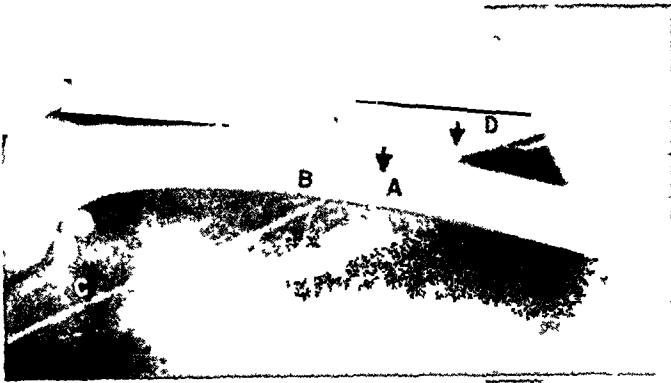


FIG 10



FIG 11



FIG 9—A lucite tube in the femoral artery on the fourth postoperative day. The arrows indicate the extent of the tube. (A) Demonstrates the clot almost completely occluding the distal end of the tube. (B) Shows an embolus at the bifurcation of the femoral artery completely blocking the anterior tibial artery and protruding into the popliteal artery. (C) Another small embolus in the popliteal artery. (D) Shows the narrowing of the femoral artery proximal to the tube and the development of collateral circulation which follows thrombosis of these tubes.

FIG 10—The lucite tube in Figure 9, 24 hours later showing complete thrombosis and further development of collateral circulation.

FIG 11—The other leg of the animal in Figures 9 and 10 showing the collateral circulation 48 hours after complete thrombosis of the tube.

to and enveloped the plastic tubes in a fibrous sheath of slight to moderate thickness with no discernible difference between the two plastics used

B Arterial ligations

With the same operative destruction of collateral circulation as in the intubation technics, the two animals with femoral artery ligation had cold legs for about 24 hours and negative oscillations for about two weeks. After the 24-hour period following operation the collateral circulation developed as with the arterial intubations. Propagation of clots in the first few postoperative days was negligible with both ligation and intubation technics, but with the passage of weeks propagation from the tube thrombi seemed to be somewhat greater than following either type of arterial ligation.

C Intima coaptation technics

Examination of a suture anastomosis of the femoral artery at the end of a week showed complete patency with no fibrin deposition or clotting and the beginning of intima-to-intima union. In an anastomosis using venous-lined polyethylene tubes, roentgenograms showed patency at the end of a week. At the end of three weeks the tube was free of clots and the union between venous and arterial intima was complete. Reaction to the polyethylene tube, however, had thickened the venous wall and nearly occluded the lumen at the proximal tube-vessel junction.

DISCUSSION

The fact that some aortic intubations remain patent permanently whereas ✓' all femoral intubations clot about the third day may be explained in several ways. The pattern of blood flow in the aorta depends among other things upon the diameter of the vessel and the velocity of flow. Both of these factors vary in systole and diastole. The density and absolute viscosity of the blood, which also influence flow patterns, may or may not be constant. In spite of these variables, numerical values have been substituted in the formula for the Reynold's number. The figure obtained for the Reynold's number during systole in the thoracic aorta of dogs is well above 2000, the critical level where laminar or viscous flow becomes turbulent in smooth pipes. The irregularity at the tube-vessel junctions further predisposes to turbulence.^{17 17} Assuming that the values are correct, the significance of this higher velocity and possible turbulence in the aorta, as opposed to the femoral artery and smaller vessels, lies in the concomitant increase in the erosive power of the blood stream on freshly formed clots, since the shearing stress between circulating blood and vessel wall varies with the velocity and is much greater for turbulent than for laminar flow.^{†16} Another of the possible explanations is that the large volume flow in

✓ The Reynold's number equals the velocity of flow multiplied by the diameter of the vessel and divided by the kinematic viscosity of the circulating fluid. Kinematic viscosity equals the absolute viscosity divided by the density of the fluid.¹⁵

† The fact that the shearing stress also varies inversely with the diameter of the vessel is of less importance in this range of velocities and Reynold's numbers.

the aorta may dilute or remove more effectively the locally liberated substances which promote clotting

These considerations may explain the embolic phenomena observed frequently following the aortic anastomoses with polyethylene tubes as well as the capacity of these anastomoses for remaining open permanently. They also emphasize the important influence of the vessel size on the duration of patency of an anastomosis and qualify the apparent superiority of the larger lucite tubes over the smaller polyethylene tubes in the aortic and arterial anastomoses. In addition, these concepts modify the predictions of efficacy of these femoral intubations in the larger arteries of humans. This does not mean, however, that the results in the aortas of dogs can be extrapolated to the similar sized femoral arteries of man, since the pressure gradients (and hence velocities) are different in central and peripheral vessels.

Besides the arterial size, other technical factors which influence the duration of patency are (1) The inner smoothness, over-all symmetry, and suitable size of the tube, (2) the intrinsic capacity of the tube for repelling water and delaying coagulation and (3) the amount of trauma to the arterial intima during insertion.

Although fatal hemothorax was a common complication in the aortic intubations, secondary hemorrhage following intubations of the femoral artery was a rare complication and usually due to tubes excessively large for the artery under repair. The greater retraction of the elastic tissue in the wall of the aorta and the higher pressures in the upper aorta (especially with a thrombus occluding the tube) probably increased the strain on the ligatures and contributed to the aortic ruptures.

Although the plastic tubes in the femoral arteries were thrombosed after two days, their gradual occlusion stimulated collateral circulation and avoided the temporary period of acute ischemia which followed arterial ligation. The marked stimulus to collateral circulation of the tube anastomoses was also demonstrated by the animal with an aortic anastomosis which maintained blood supply to the abdominal aorta sufficient to sustain normal function despite complete thrombosis of the tube and extensive operative destruction of collateral circulation.

The greatly prolonged durations of patency of the suture anastomosis and venous-lined polyethylene tubes show the superiority of these methods over the plastic tube anastomoses with respect to avoidance of thrombosis. Experienced vascular surgeons can obtain about 50 per cent permanent patencies with suture anastomoses of the dog's femoral artery. Blakemore has reported that his nonsuture method using venous-lined vitallium tubes is 85 per cent successful in day-old contaminated wounds in dogs, as compared with 40 per cent patency following suture anastomosis under these conditions.²

These facts plus the high percentage of thromboses which followed the Blakemore reparative technic in arterial injuries of the last war point up the difference between the results of intubations done under the ideal circumstances

of the experimental laboratory and those done under battle conditions. In battle injuries to arteries repaired with plastic tubes, assurance of patency of the anastomoses beyond the period of post-traumatic edema would seem, from these considerations, to require supplementary anticoagulant therapy.

III. INTRA-ARTERIAL HEPARIN ADMINISTRATION

MATERIALS AND METHODS

Description of the tubes The polyethylene tubes and the intubations of the femoral arteries were the same as described in the preceding section.

Heparinization Intra-arterial heparin was infused proximal to the anastomosis by the same route that 35 per cent diodrast was injected for the arteriograms described previously, *ie*, through a subcutaneous polyethylene side tube from the skin of the costovertebral area to the lumen of the long saphenous artery (Fig 6). Sodium heparin, Lederle, (0.25 mg per Kg of body weight in 10 cc of saline) was given shortly after operation into the left femoral artery and repeated every two hours, in some animals every three hours, day and night. The right side tube was used only for postoperative arteriograms. Unlike human beings with arterial injuries, dogs continually move about following operation, and unless the side tube has a relatively thick wall, it will kink and leak after a few days of heparin administration. The side tubes in this preliminary study of intra-arterial heparinization were too thin, and in most instances subcutaneous leakage of heparin necessitated cessation of therapy about the fifth day. A thicker side tube is now being used (0.4 mm i.d. and 1.0 mm o.d.) which is attached to the main tube in a manner that eliminates the necessity of intubating a branch of the femoral artery, thereby simplifying the operative technic and sparing another artery for collateral circulation.

Postoperative observations The follow-up observations were made with oscillometry and periodic arteriograms in the manner described previously. The anastomosis of the uninjected artery reflected the systemic effect of the intra-arterial heparin administration and the irrigated intubation showed the combined local and systemic effect of the heparin. By contrasting the results in the two femoral intubations, the local effect of heparin could be evaluated in a series of animals.

Since dogs as well as human beings vary in their responses to a given dose of heparin, coagulation times were done preoperatively and at intervals postoperatively to evaluate the daily heparin effects in these animals. Investigators in this field have been impressed with the inadequacies of coagulation times in evaluating the effect of heparin. Control clotting times vary widely even in the same animal from time to time. One of the factors responsible is the varying amount of trauma incident on transferring blood from the animal's vein to the tube. Another factor is the ambiguous nature of most endpoints. In addition, the actual fluidity and coagulability of the blood probably varies normally from time to time according to the relative concentrations of heparin and

thromboplastin (and other clotting substances) in the circulating blood^{18 20} The concentration of heparin cofactor in the plasma may also vary and thus alter the response to a given dosage of heparin^{21, 22}

An attempt was made to control the first factor by letting the blood flow freely through a No 20 B-D needle with exclusion of air into the clean syringe lined with liquid petrolatum after uniformly direct venepunctures The sample was then transferred carefully to a glass tube of 5 mm i d, bent in the form of a semicircle of 6 cm radius²³ This tube was moved uniformly at definite intervals until complete clotting occurred In an attempt to make the end-points more precise the times of the earliest definite fibrin precipitation and the complete immobility of the blood in the tube were measured by stop watch

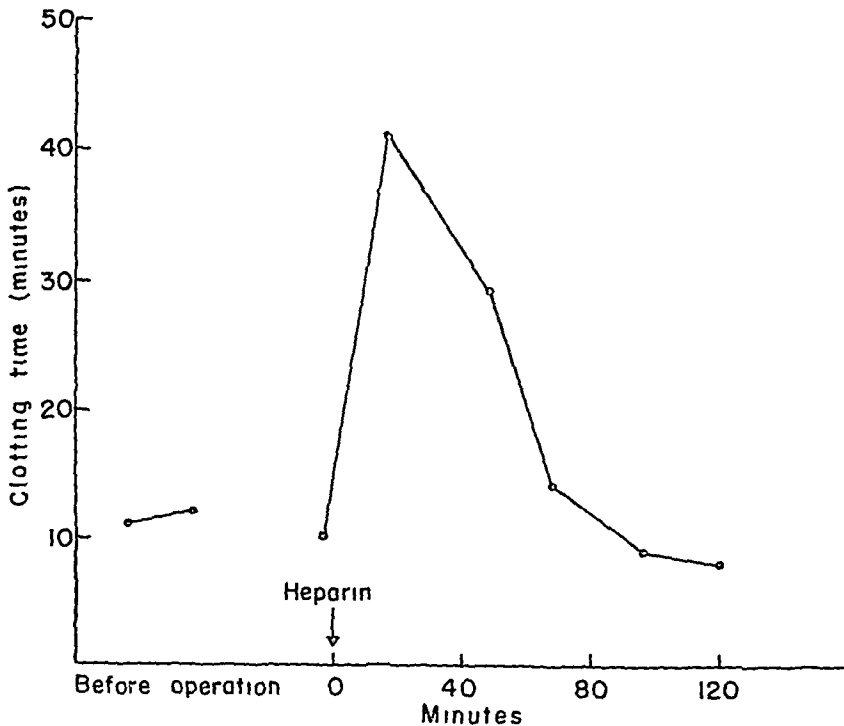


FIG 12—The response of the venous clotting time to the intra-arterial injection of 4 mg of sodium heparin in 10 cc of saline in a 16 Kg dog

and these two durations averaged to determine the clotting time for each sample Since it has been repeatedly emphasized that both phases of coagulation are proportional in length, the average of the duration of the first phase (prothrombin conversion to thrombin) and the duration of the first plus the second phase (fibrinogen conversion to fibrin) should give a more reproducible value for the coagulability of each sample²³

RESULTS

The above procedures have been done on eight dogs Only two will be reported here because technical difficulties made the results in the other animals hard to interpret, although the general pattern of reactions was similar

Dog 1 (16 Kg) Four mg of sodium heparin was given in 10 cc of saline into the left artery every two hours for 120 hours, until subcutaneous leakage necessitated cessation of therapy. Four of the 60 doses scheduled were omitted, leaving a total of 216 mg of sodium heparin in 540 cc of saline given during this period. Figure 12 shows the marked prolongation of coagulation time caused by 0.25 mg heparin/Kg of body weight on the first day. This response became less marked during the next four days.

The left or heparinized artery was patent on the fourth postoperative day (Fig 13). The right or control artery was open by arteriography on the third day but thrombosed on the fourth postoperative day. The right or control artery exceeded the average duration of patency in polyethylene intubations of the femoral artery by about 24 hours. The left or heparinized artery exceeded the average duration of patency by at least 48 hours.

Dog 2 (24 Kg) Six mg of sodium heparin was given in 10 cc of saline into the left artery every three hours for 114 hours until leakage from the side tube prevented further therapy. These 38 injections totaled 228 mg of heparin in 380 cc of saline. The clotting time response to this 0.25 mg of heparin per Kg of body weight was slight (not more than double the control level) throughout the period of heparinization.

The left or heparinized artery was patent on the fourth postoperative day (Fig 14). Oscillations remained about 2 plus until the seventh postoperative day. The right or control anastomosis was patent by roentgen ray on the second day and thrombosed on the third postoperative day. The right or control artery had the same duration of patency as the average of polyethylene intubations in unheparinized animals. The left or heparinized anastomosis exceeded this average duration of patency by at least 48 hours and possibly by 96 hours.

DISCUSSION

Intravenous anticoagulants are often contraindicated in war wounds, since the latter are frequently multiple and complicated by latent visceral bleeding. Furthermore, the administration and control of anticoagulants are often imprac-

FIG 13



FIG 14

FIG 13—The roentgen-ray of the heparinized artery of the animal in Figure 12 on the fourth postoperative day. Arrows indicate the ends of the polyethylene tube and X, a leak in the side tube which prevented further intra-arterial heparin administration on the fifth postoperative day.

FIG 14—An arteriogram of the heparinized femoral artery on the fourth postoperative day. Arrows indicate the ends of the polyethylene tube and X, a leak in the side tube which prevented further intra-arterial heparinization on the fifth postoperative day.

tical under battle conditions. It occurred to the author that heparin might be given intra-arterially proximal to the anastomosis with constant or intermittent infusions in concentrations which would prove effective locally and yet not raise the general clotting time to a dangerous level. Heparin was chosen for intra-arterial use, because it is a potent, physiologic anticoagulant which acts instantly in a physicochemical manner²⁰. It is also rapidly inactivated by nontoxic protamine sulfate given intravenously.

Although these investigations are still in progress, using a different method of intra-arterial heparin administration, two cases have been presented since they represent the general pattern of the results to date.

Although the clotting time responses to intra-arterial heparin injections in dog No. 1 became less marked with each succeeding postoperative day, the control artery seems to have obtained some systemic heparin effect, since it exceeded the average duration of patency by about 24 hours. The left or heparinized side remained patent even longer and appears to have had an added local effect.

A lack of systemic heparin effect is indicated by the clotting time studies in dog No. 2, which received the same 0.25 mg. of heparin per Kg. of body weight every three hours instead of every two hours as in dog No. 1. This lack of general effect is further evinced by the thrombosis of the un.injected artery in the usual length of time. A significant local effect is suggested by the greatly prolonged patency of the left or heparinized anastomosis.

These two examples suggest a definite local action of the intra-arterial heparin in doses not generally effective or dangerous. Although these are typical of other results, the statistical proof of this idea awaits further investigation. Furthermore, the mechanical effect of local irrigation must be ruled out by injecting similar amounts of saline without heparin in the control arteries.

Bleeding into the incision was the only complication of this technic, and its rare occurrence was due to copious leakage of heparin subcutaneously. If this route of heparin administration proves effective, it may be equally advantageous to give vasodilators in this manner, thereby delivering the various agents to the important arterioles of the muscles and deeper structures, and inducing a local hyperemia by dint of the borrowing-lending mechanism of blood distribution.^{24, 26} Antibiotics may likewise prove more effective by this route.

SUMMARY

1. In a preliminary study the reaction to pure polyethylene in the subcutaneous tissues of rats was similar to that caused by the relatively well tolerated lucite. The capacity of the polyethylene surface for delaying the *in vitro* coagulation of blood was also found to be similar to lucite, being about twice that of glass and nearly as great as paraffin and collodion. Surface tension studies in glass and polyethylene tubing showed that polyethylene, like lucite, follows Lampert's rule that the capacity of a surface for delaying coagulation is inversely proportional to its "wettability."

2 Polyethylene tubes were used to bridge gaps in the thoracic aorta of dogs after the method of Hufnagel

In an initial group of 14 anastomoses, two polyethylene tubes remained patent for periods of 9 and 12 months when the dogs were killed. Half of the deaths in this group were due to aortic rupture with fatal hemothorax. In a second series of nine intubations, five animals were apparently healthy at the end of three months. Two of these five later developed fatal mesenteric embolism following aortograms with large doses of intravenous thorotrast. Two remained well for periods of six and eight months when they were killed.

Of the four permanent intubations one was completely patent 12 months postoperatively, two were partially thrombosed, and one was completely thrombosed. Marked enlargement of collateral pathways sustained normal function in the dog with complete thrombosis.

3 Anastomoses of the femoral artery with lucite and polyethylene tubes were performed with a new instrument for facilitating the insertion of artificial tubes. They were followed by frequent oscillometric examinations and daily arteriograms. The anastomoses with plastic tubes were compared with arterial ligations, suture anastomosis, and an anastomosis with venous-lined polyethylene tubes.

✓ The average duration of patency of the polyethylene tubes was two days, while the slightly larger lucite tubes remained patent for three days. This average period of patency in polyethylene intubations was not prolonged by lining the tubes with silicone or soaking them in heparin preoperatively. During and after thrombosis of these tubes abundant collateral circulation developed and the limb was never acutely ischemic. Conversely, the animals with arterial ligations developed markedly ischemic limbs for the 24-hour period following ligation. The intima coaptation technics were much superior to the plastic tube anastomoses in respect to the avoidance of thrombosis. Since these more physiologic technics are usually impractical under battle conditions, further study of the simple anastomoses with plastic tubes was undertaken using supplementary anticoagulant therapy.

4 Because intravenous anticoagulants are contraindicated in most war wounds, study was initiated on a method for giving intra-arterial heparin proximal to the anastomoses of the femoral artery. The heparin was infused through the left side tube used for postoperative arteriograms and the right or uninjected artery acted as a control. Venous clotting times were also done to evaluate the systemic effect of the intra-arterial heparin. Typical cases were presented to indicate the kind of results which have occurred to date. They suggest that an adequate local effect may be achieved without prolonging the general clotting time significantly.

CONCLUSIONS

1 Pure polyethylene, like lucite, is relatively well tolerated in the tissues surrounding the femoral artery of dogs and in the subcutaneous tissues of

dogs and rats The mediastinal tissues of dogs also showed slight to moderate reaction to pure polyethylene

2 Polyethylene has a capacity for delaying the *in vitro* coagulation of blood which is similar to that of lucite, being about twice that of glass and nearly as great as paraffin and collodion

3 Polyethylene repels water relatively well and, like lucite, follows Lempert's rule that the capacity of a surface for delaying coagulation is inversely proportional to its "wettability"

4 Polyethylene tubes will permanently bridge gaps in the thoracic aorta of dogs Many of these anastomoses, however, are complicated by thrombosis, embolism, and aortic rupture

5 Anastomoses of the femoral arteries of dogs with polyethylene and lucite tubes have average durations of patency of two and three days, respectively Lining the polyethylene tubes with silicone or saturating them with heparin preoperatively did not increase the average duration of patency

6 A new instrument for retracting the walls of arteries facilitates the insertion of these artificial tubes

7 Although the plastic tube anastomoses are inferior to intima coaptation technics in respect to the avoidance of thrombosis, their gradual occlusion over a period of days stimulates collateral circulation and prevents the marked ischemia which follows arterial ligation

8 In battle injuries to arteries repaired with plastic tubes, assurance of patency of the anastomoses beyond the period of post-traumatic edema would probably require supplementary anticoagulant therapy Although intravenous anticoagulants are usually impractical in war wounds, a new method for the intra-arterial administration of heparin has shown promise and merits further study

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ACUTE PANCREATITIS*

A CLINICAL EVALUATION AND REVIEW OF 154 CASES

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TWENTY YEARS AGO, one of us had the opportunity of reviewing 88 cases of acute pancreatitis with Dr William Linder³⁵ The present analysis includes an additional 66 cases, a total of 154 cases operated upon between 1913 and 1948 In our paper of 1929, we stressed the importance of diagnosis before abdominal section The former concept, that acute pancreatitis can only be diagnosed at the operating table, is no longer true Fitz indicated that this abdominal catastrophe should be suspected whenever violent epigastric pain is followed by vomiting and collapse This occurs in fulminating cases Little can be learned or done about this type, but acute pancreatitis, if borne in mind whenever an acute abdominal mishap presents itself, offers no greater difficulty in diagnosis than any other surgical condition

The pathogenesis of acute pancreatitis, its differential diagnosis and treatment, will be discussed in some detail The accompanying tables are meant to convey the pertinent statistical findings in the 154 cases analyzed

ETIOLOGY

Acute pancreatic disease may be infectious or noninfectious The proponents of the infectious theory point out the possibility of extension of infection along the lymphatics, by pyemic involvement via the blood stream, by direct contiguity, by extension along the pancreatic ducts from the duodenum or bile ducts, by activation by bacteria in the normal pancreas, or finally, by bacterial permeation from adjacent altered viscera

In this connection, it may be of some interest to note that neither Truhart,⁵³ in 43 cases, nor Jones³⁰ found bacteria present in the pancreas When we realize how infrequently acute pancreatitis is encountered in conjunction with perforation of duodenal or gastric ulcers into the pancreas, the rarity of the incidence of infection by contiguity becomes apparent

Infection may be a potent factor indirectly In late cases, the bacteria most frequently isolated are *E Coli*, pneumococcus and staphylococcus Brocq⁸ cultured anaerobes from the gangrenous variety, but the necrotic type was sterile Experimentally, Carnot,¹⁰ and Korte³² produced acute pancreatitis by injecting colon and pyocyaneus bacilli, and other bacteria into the pancreatic duct Archibald² produced fatal pancreatitis by colon bacillus injection Kemp³¹ stated that certain bacteria, especially of the typhoid and colon groups, are capable of activating proteolytic pancreatic enzymes

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Lymphogenous infection from the gallbladder, liver and appendix has been emphasized in both acute and chronic pancreatitis by Maugeret,³⁷ Arnsperger,⁴ Deaver,¹⁵ Graham²⁶ and others, but whereas most observers agree that this may be the *modus operandi* in the chronic type, the acute process has never been produced experimentally in this manner

Jones³⁰ believes chronic pancreatitis to be the result of interstitial tissue inflammation produced by lymphatic extension, whereas acute pancreatitis involves the parenchyma via the pancreatic ducts

Gastro-intestinal infection may reach the liver through the portal system and thence extend to the pancreatic gland

Hematogenous pancreatitis through bacterial metastasis is rare, but pancreatic inflammation has been reported in conjunction with epidemic parotitis and infectious thrombophlebitic processes

Rosenow,⁴⁷ experimentally, produced cholecystitis and pancreatitis by injecting intravenously streptococci obtained from the tonsils of patients with gallbladder symptoms

The non-infectious theory presupposes first, mechanical stasis, and second, the chemical activation of inactive ferments resulting from autolysis of bile, duodenal contents or degenerated duct contents. Although associated biliary disease is a concomitant finding in the majority of cases, those without apparent cholecystitis must be explained. In these, toxic products may develop within the pancreas or may be regurgitated from the biliary tract or duodenum into the pancreatic ducts

Inactive pancreatic juice is harmless. Experimental ligation of the pancreatic duct produces no necrosis. If, however, ligation be effected at the height of digestion, pancreatic necrosis ensues. Section of the duct, with escape of inactive juice into the peritoneal cavity, produces neither pancreatic involvement nor clinical symptoms. Simple pancreatic injury fails to produce necrosis, even though activating substance may be liberated

Levin³³ crushed the pancreas when associated blood vessel occlusion existed and produced characteristic hemorrhagic necrosis. Clinically, trauma has frequently been followed by acute pancreatitis

Bile for many years has been recognized as a factor in the production of acute pancreatitis. Bradley and Taylor⁷ found that bile did not activate the enzymes. Others believe that bile merely accelerates the action of the pancreatic ferments. When bile was brought into contact with the pancreas, acute hemorrhagic pancreatitis resulted. It has been demonstrated that injection of small amounts of bile into the duct of Wirsung produces acute pancreatic disease, if done at the height of digestion. Opie⁴¹ found that considerable amounts of bile were necessary. Nordmann⁴⁰ produced very little reaction with sterile bile, but infected bile was more potent in the production of pancreatic necrosis. Sodium taurocholate appears to be the offending substance. It is found in abundance in infected bile. Focal liver necrosis is noted early in acute pancreatitis

According to the regurgitation theory, three factors are involved in the production of acute pancreatitis. First, a change in bile composition, second, undue resistance, such as is produced by stone or spasm, and third, elevation of gallbladder pressure or bile duct pressure sufficient to produce reflux of bile into the pancreas.

Clinically, bile may enter pancreatic ducts following obstruction of the common outlet in cases where bile and pancreatic ducts join, or by regurgitation of duodenal contents.

Here a few anatomical observations may not be amiss. Mann and Giardano³⁶ found that in only 3.5 per cent of subjects did the anatomic arrangement of bile and pancreatic ducts permit of common channel production. Cameron and Noble⁹ concluded that in 75 per cent of individuals a calculus impacted at the papilla could produce a common passageway. It should be recalled that stones were found in the ampulla in but 5.4 per cent of 1287 cases, one of these the celebrated case of Opie, operated upon successfully by Halstead. It served, however, as an impetus to the study of pancreatitis.

Zuckerkindl⁶¹ found that the accessory and main pancreatic ducts usually communicate by a wide opening, close to the duodenal end. Opie⁴¹ found this situation in 90 of 100 dissections. Baldwin⁵ found that the common duct opened separately into the duodenum in 25.8 per cent and in a common ampulla in 74.2 per cent.

Obstruction may be due to stone, spasm, inflammatory swelling, mucus, parasites, and even venous congestion due to cardiac decompensation. Spasm can be induced by dilute hydrochloric acid in the duodenum. It is also increased by gastroduodenitis and dietary indiscretion.

Duodenal contents in the absence of infection may produce acute pancreatitis. Polya⁴² accomplished this by injecting small amounts of duodenal contents into the pancreatic duct. In support of the duodenal-origin hypothesis is a large number of cases where biliary disease is not apparent. Regurgitation may occur in acute or chronic dilatation, or aided by antiperistalsis, in the presence of a relaxed or dilated sphincter of Oddi.

Brocq⁸ completely obstructed the duodenum following gastroenterostomy and produced pancreatic necrosis. Seidel⁵⁰ accomplished the same by causing stasis in the duodenum. Opie suggested the presence of delicate valves in the diverticulum of Vater, that normally prevent regurgitation.

Brocq suggested that predominance of the hemorrhagic feature in acute pancreatitis is the result of the activation of trypsin by regurgitated duodenal contents, while preponderant fat necrosis is due to bile regurgitation.

Substances that have been utilized to produce acute pancreatitis experimentally are diphtheria toxin, acid gastric juice, alkalis, calcium chloride, formaldehyde and leucocytes with bacteria.

Rich and Duff⁴⁵ have described a peculiar hyaline necrosis of the walls of the pancreatic arteries and veins in acute pancreatitis. They believed necrosis to be the initial lesion, and to be due to the extravasation of active trypsin.

They observed a remarkable metaplasia of the pancreatic duct epithelium in 13 of 24 cases examined, and since reflux of bile, infection and obstruction account for but two-thirds of the cases, they suggested that duct obstruction caused by this proliferation might be responsible for escape of trypsin, and consequently of hemorrhagic pancreatitis by thrombus and hemorrhagic production

Inspissated secretion in the pancreatic ducts appears to be another cause. Acute pancreatitis may be encountered concomitant with degenerative pancreatic processes such as tumors, vascular degeneration, toxic changes in systemic disease, and trauma

Clinically, acute pancreatitis is not a primary disease, but rather a complication or sequela. Whether we subscribe to one or another of the hypotheses, the realization that biliary disease is so frequently the etiologic precursor must be evident. Egdahl's¹⁹ incidence of biliary calculi in 50 per cent and cholecystitis in 75 per cent is not mere coincidence. Where no biliary disease is apparent, it is well to recall Hess's²⁹ work. He produced acute pancreatic necrosis by ligating the pancreatic duct at the height of digestion. Pratt⁴³ did the same in fasting animals with no resultant necrosis. Notwithstanding all the possible methods of, and etiologic factors in the production of acute pancreatitis, we may assume the great majority to be due to biliary disease. Certainly these latter cases are those with which we are most frequently confronted.

Fat necrosis has been taken as the diagnostic criterion of the 154 cases herein analyzed. That acute pancreatitis does exist without fat necrosis has been proved clinically, but it was deemed advisable to include only those cases in which fat necrosis was demonstrable to prevent the possible inclusion of doubtful cases.

CLASSIFICATION

There is ample justification for considering acute edematous or interstitial pancreatitis as a milder grade of acute pancreatic necrosis, which may be predominantly hemorrhagic, necrotic or suppurative. Quick⁴¹ operated upon a patient with edematous pancreatitis only to find two days later that she succumbed to extensive pancreatic necrosis as demonstrated at autopsy. Cole's¹² work offered corroboration by the finding, in six cases of acute pancreatic edema, of a sharp rise in blood amylase, a very significant observation in all forms of acute pancreatitis.

INCIDENCE

Seventy-six per cent of our cases involved females. The female-male ratio was the same in acute pancreatitis as in our cases of gallbladder disease, though Riese's⁴⁰ and Korte's³² observations were to the contrary. The former observed males predominating, 79 to 42, the latter 30 to 14. If we regard biliary disease as the important etiologic factor, males and females are alike affected. Forty-five cases herein included occurred in a period during which

2049 cases of biliary disease were submitted to operation, an incidence of approximately 2 per cent

Fifty per cent of our cases occurred in the fourth and fifth decades. The youngest patient was 19, the oldest 73.

Previous gastro-intestinal disorders are of considerable significance. All but 19 gave a history of some form of "dyspepsia" and of these, six had had repeated alimentary disturbances for three to four weeks prior to hospital admission. Sixty-three per cent gave a definite history of biliary disease.

Alcoholism, in the literature, constitutes one of the cogent factors in acute pancreatitis. When we realize that no case is permitted to enter our institution in which alcoholism is a predominating symptom, it becomes apparent why this series contains no case in which alcoholic diathesis plays any role.

PATHOGENESIS

Pancreatic symptomatology in its acute manifestations depends on the activation of trypsinogen into trypsin. Physiologically this activation occurs in the duodenum through stimulation by succus entericus. Protein digestion by this liberated enzyme may affect blood vessels, lymph structures or pancreatic cells. Activation is furthered by the products of cytolysis and by the calcium of extravasated blood serum. The liberated trypsin destroys protein molecules which have been combined with bile salts, thus setting the latter free to produce further cell damage. The resultant edema and sanguination may be extensive and severe in a very short time. If the process terminates at this stage, complete restitution may ensue. Progression may result in local or diffuse necrosis of the entire parenchyma.

Circulation of foreign protein in the form of incomplete protein digestion products may in part serve to explain the severe toxic picture. Some believe the significant product of proteolysis to be histamine, produced in the necrotic tissue or in the peritoneal fluid. Dragstedt¹⁷ showed that intraperitoneal fluid and products of pancreatic autolysis, when injected, were not toxic. However, when these were infected, the characteristic symptoms developed. Experimental intravenous injection of peritoneal fluid from cases of acute pancreatitis by Cooke and Whipple,¹³ was without toxic effect.

Blood vessel digestion contributes the hemorrhagic features. Peritonitis is due to toxic products circulating in the subserous lymphatics. Thus, the entire syndrome depicts a definite clinical entity that can be recognized.

Fat necrosis in acute pancreatitis may involve the fat of the abdominal wall, pericardium or pleura. The dissemination of this necrosis depends on the circulation of lipase in the blood. Wood⁶⁰ suggests that the activation of steapsinogen in the pancreas is by some constituent of the bile, and Flexner²⁴ demonstrated a fat splitting enzyme in necrotic foci. Splitting of a fat into soluble glycerin and fatty acid results in deposition of the latter as crystals, which later, with calcium, form globular masses surrounded by zones of round cell infiltration. Wells⁵⁷ found that a moderate amount of these necrotic areas might be absorbed in a week.

Digestion of pancreatic cells liberates their contained trypsin and lipase, and consequently not only these two enzymes, but the products of their complete and incomplete digestion as well, are circulated through the lymph channels. Therefore, symptoms of acute pancreatitis are due first to local pancreatic irritation, and second to the circulation of toxic products.

SYMPTOMS AND SIGNS

Pancreatic inflammatory reaction results in edema and swelling, with resultant stretching of the pancreatic capsule. This causes pain and obstructs diaphragmatic excursion. Bile drainage becomes impeded by common duct obstruction. Pressure on the abdominal brain, the celiac plexus, must be considered in the explanation of acute pancreatic symptomatology at least in so far as local manifestations are concerned.

Of all the symptoms, constant epigastric pain is most frequently encountered. This pain is splitting in character, "as though something within were boring its way through." The localization of pain in this series is shown in the accompanying Table I. Pain in acute pancreatitis is of intense severity. Morphine in repeated doses fails to relieve it. It is interesting to note that patients volunteer the information that a hypodermic injection has failed to ease their discomfort, whereas during previous attacks, relief had been immediate from one dose of narcotic.

Vomiting is a troublesome, persistent complaint. However, it is never progressive and never fecal. One gastric lavage usually suffices for relief, a differential feature from high intestinal obstruction. Coffee ground or bloody vomitus may occur, and is easily explicable when one considers the proximity of the stomach to the hemorrhagic pancreas.

Protein split products introduced into the circulation call forth a peculiar train of symptoms designated allergic or anaphylactic. At times these symptoms predominate. Shock, collapse, cyanosis, dyspnea, and in some instances, dermatologic reactions (urticaria) occur. The significance to the clinical picture of pressure on the celiac plexus can merely be mentioned, but Whipple⁵⁸ pointed out a peculiar asthenia characteristic of pancreatic disease. Cyanosis may in part be due to diaphragmatic embarrassment resulting from local pancreatic swelling.

Temperature plays little, if any, role in the diagnosis. Jaundice may be due to local pancreatic pressure on the ductus choledochus. It is never severe. Concomitant liver necrosis may influence the degree of jaundice, as will the presence of stones in the common duct. Acute yellow atrophy has been found as a complication of acute pancreatitis.

Peritonitis, whether bacterial or chemical in origin, produces the same symptoms, local or diffuse. Local peritonitis due to mechanical stretching of the peritoneum over the pancreas adds the local objective signs to the diffuse ones caused by the chemical irritant.

Constipation is not uncommon. Diarrhea, when it occurs, is usually a late manifestation indicating considerable pancreatic destruction. Constipation is

not complete, a fact of value in differentiating low intestinal obstruction. The silent paretic abdomen of acute pancreatitis offers a marked contrast to the abdominal findings in mechanical obstruction. Turner⁵⁴ described a bluish-brown discoloration of the skin overlying the left flank and back. This has never been seen by us. He also mentioned the diagnostic value of the para-umbilical skin discoloration, which was similarly lacking in our series (Cullen's sign).

Statistical resumé's help but little in the diagnosis of acute pancreatitis. However, when a patient with a history of gallbladder disease presents a somewhat altered symptom complex, if morphine fails to alleviate the pain,

TABLE I—*Pain in Acute Pancreatitis (154 Cases)*

Location	Percentage
Epigastric	87%
Right hypochondriac	61
Left hypochondriac	28
Left lumbar	54
General abdominal	30

which now radiates from epigastrium transversely to the left, if cyanosis and slight icterus, together with a peculiar asthenia and dyspnea occur, acute pancreatitis must be considered. Tenderness over the left hypochondrium and left costo-vertebral area should strengthen the clinical impression.

Tables I and II depict the location of pain and tenderness in our present series. In Table III, the more pertinent signs and symptoms, other than pain, are indicated.

TABLE II—*Tenderness in Acute Pancreatitis (154 Cases)*

Location	Percentage
Epigastric	58%
Right hypochondriac	59
Left hypochondriac	30
Left costovertebral	37
General abdominal	26

DIFFERENTIAL DIAGNOSIS

Symptomatology must be clearly analyzed, for acute pancreatitis may simulate other acute abdominal entities. Acute empyematous cholecystitis may be troublesome in the differential diagnosis. This is especially true when impending perforation and local peritonitis exist. The presence of a palpable mass which attaches itself to the lower border of the liver aids greatly. Pear-shaped or globular, this mass denotes a distended gallbladder due to cystic duct block. Irregularity or boggy-ness of the mass may be caused by adherent omentum protecting an impending blow-out, or an already perforated gallbladder. Because of its superficial position, light palpation performed by placing the

palm of the hand on the abdomen with the patient breathing slowly and deeply, easily discloses the mass. It is significant that only 7 per cent of our cases of acute pancreatitis had acute cholecystitis at the same time.

Perforation of a diseased gallbladder into the general peritoneal cavity produces shock simulating that of acute pancreatitis, but the differential diagnosis may be made by the history of a previously distended, acutely inflamed gallbladder, where medical treatment failed to relieve the cystic duct block. Gallbladders do perforate, but if the sudden onset of acute pancreatitis is borne in mind, and the local findings enumerated above are absent, a correct diagnosis can be made.

Acute intestinal obstruction, especially the high variety, may offer some difficulty. Although the shock produced by the sudden snaring of a loop of gut by a band or internal hernia may be great, the early visible peristalsis, the progressive vomiting, the painless abdomen, the absence of epigastric and left costovertebral tenderness and the absent malar flush, all assist in making a correct diagnosis.

TABLE III—*Other Symptomatology (154 Cases)*

	Percentage
Cyanosis	45%
Shock	17
Emesis	88
Abdominal distention	56
Jaundice	27
Urticaria	3

Left renal colic, particularly when attended by extreme pain and shock, offers some difficulty. If radiation of pain to the groin is absent, acute pancreatitis must be considered. Pyuria or the presence of erythrocytes in the urine certainly help. Sudden torsion of a ptotic kidney with renal pedicle strangulation simulates pancreatitis. The history of ptosis in a patient with considerable weight loss and the picture of Dietl's crisis following sudden exertion supports the diagnosis. The kidney may be readily felt, and found enlarged and tender, if it is palpated in the lumbar region. If it is displaced to the midline its mobility can be demonstrated, and it may be repositioned in the lumbar fossa.

Tenderness in the left inguinal region, a definite Head zone, is not infrequent in acute pancreatitis, particularly when considerable bloody fluid is present in the peritoneal cavity.

Acute carbuncle of the left kidney calls for discriminatory analysis. Here, the antecedent history of some focal infection, coupled with sudden onset of chill, rise in temperature, tenderness and spasticity in either lumbar region, occurring in an otherwise healthy individual, even in the absence of pertinent urinary findings, are differential characteristics. If the anterior surface of the nephros is the site of adhesions to the parietal peritoneum, there may be added

confusion with acute pancreatitis. However, the toxemia, the shock, the flush, the paretic abdomen and the characteristic epigastric tenderness are missing.

Perforated peptic ulcer with its antecedent ulcer history, board-like rigidity and scaphoid abdomen, may well be distinguished from the pancreatic paretic abdomen. The absent mid-epigastric tenderness, the early signs of spreading peritonitis, the obliteration of liver dullness, with roentgen ray evidence of air under the diaphragm, the expiratory grunt and the absent malar flush exclude pancreatitis. The ulcer patient usually presents a characteristic facies, the long, thin, drawn, dyspeptic countenance portraying chronic pain.

Coronary and cardiac disease demand consideration. Careful precordial examination is essential, for the manifestations of heart disease are protean, and they may well simulate intra-abdominal catastrophes. A pre-existing cardiac history, with liver tenderness due to right coronary closure, upper abdominal rigidity, and an extremely hypersensitive abdominal wall, will lead to the correct diagnosis.

Acute appendicitis should give no difficulty, even when spreading peritonitis is present.

LABORATORY AIDS

What are the laboratory aids that may be utilized? The total and differential leucocyte counts of the blood are of little value. In fact, it may be stated that the importance of the white cell count in acute abdominal conditions is probably over-emphasized. Infection, hemorrhage, shock, and dehydration influence it. It should be used merely as corroborative evidence. Acute abdominal pain produces leucocytosis.

The erythrocyte count is usually high, over 5 million. Hemoglobin content, too, is elevated because of the dehydration. Increased hemoglobin may be utilized as an index of the severity of shock, and should considerably influence the surgeon as to the advisability of immediate operative intervention. Serial determinations should be made frequently in order to determine the necessary fluid requirements for the restoration and maintenance of normal blood volume.

Blood enzyme determinations should be performed early, and frequently repeated. The serum amylase test is of great value (especially early in the disease). Its determination can be carried out rapidly, and elevation of amylase levels occurs early. The lipase determination has greatest value after the first 48 hours of the illness, and its concentration remains elevated for a longer time than that of the amylase, since the latter enzyme is excreted from the body quite rapidly. Determinations for both these enzymes when acute pancreatitis is suspected should be urgently requested. There is a definite relationship between amylase findings and clinical progress. Normal determinations may re-appear within a few days in a mild attack. Normal values indicate little or no pancreatic destruction. Following cholecystostomy, the blood amylase values in pancreatic disease return to normal rather abruptly, because of relief of pancreatic pressure. Similar subsidence may occur when

ACUTE PANCREATITIS

pancreatic necrosis is progressive. Here, destruction of parenchyma which is the source of the hyperenzymemia, prevents manufacture and liberation of the pancreatic enzymes. Hyper-cholesterolemia has been frequently reported.

The urine may manifest the intoxication by the presence of albumin and casts. Glycosuria need not be, and usually is not present. Any severe peritonitis may be accompanied by glycosuria. Urinary diastase may rise from the normal of 30 units to 200–1000.

Recently, Edmondson and Berne¹⁸ have drawn attention to the marked mobilization of calcium in and around the pancreas resulting from the formation of calcium soaps which are clinically recognized as the areas of "fat necrosis." This results in an absolute hypocalcemia which is most apparent between the fourth and tenth days of the disease. Fatal prognostic significance has been attached by them to serum calcium levels below 7 mg per 100 cc. Early serum calcium determination has little value in the diagnosis of acute pancreatitis, or where fat necrosis is very minimal.

A scout film of the abdomen may show free air under the diaphragm or fluid levels in intestinal loops, indicating perforated ulcer or acute intestinal obstruction respectively. Later, if the patient's condition permits, a barium meal may disclose a wide duodenal sweep, an irregular greater curvature of the stomach, pyloric obstruction, or a depressed transverse colon, all signs of an enlarged pancreas.

Gottesman and his associates,²⁵ and more recently, Bockus and Raffensperger⁶ have described significant electrocardiographic changes in acute pancreatitis. Improvement in the patient's clinical status is concomitant with the disappearance of these abnormal tracings. Hypopotassemia occurring in association with vomiting and/or dehydration has been ascribed as the cause for these changes by Bockus, quoting Bellet.

TREATMENT

During the past decade, therapy of acute pancreatitis has tended toward conservatism. Surgery is usually either delayed or withheld entirely. Immediate operation is justified only when the diagnosis is uncertain, when peritonitis is marked, when ileus persists without improvement, or when abscess is present. Subsequent operative intervention may be contemplated following the acute phase, especially when cholecystitis is the precursor (as it has been in practically all our cases).

If we have, with a fair degree of certainty, established the diagnosis of acute pancreatitis clinically, immediate surgical intervention avails us naught, and the added trauma may act to the detriment of the patient. The therapy should be directed to stopping the activation of trypsin within the pancreas, for, regardless of whether we believe that the mortality in acute pancreatitis results from shock, anaphylaxis, or toxemia, the basic mechanism in the evolution of the pathologic and the clinical picture is parenteral tryptic digestion. If perforated ulcer and intestinal obstruction can be definitely excluded, conservatism directed towards halting trypsin digestion is indicated.

MEDICAL REGIME

The principles of treatment which are generally employed include starvation, which markedly inhibits the secretion of tryptic ferments, continuous gastric suction, to further rest the pancreas, the relief of pain by means of opiates and by procaine injection of the splanchnic nerves, the restoration of normal blood concentration and volume, utilizing whole blood, plasma and glucose (the latter to be given with sufficient insulin "coverage" to prevent pancreatic stimulation), the prevention of distention by Miller-Abbott intubation, the inhibition of nervous stimulation of the pancreas, using atropine and ephedrine, and the recognition and elimination of hypocalcemia, utilizing calcium gluconate parenterally. Recently roentgen ray therapy has been used successfully by Chisholm and Seibel¹¹ to decrease the serum amylase in acute pancreatitis in experimental animals, and also in a small series of clinical cases.

SURGICAL TREATMENT

Surgically, five procedures have been developed as follows

1 *Pancreatic drainage*, by splitting the peritoneal covering of the pancreas or by section of the gland itself, to encourage external discharge of the necrotic material. The process in the pancreas is not ameliorated by such manipulation and pancreatic incision may enhance the danger of hemorrhage. A fatal result was reported by Walzel⁵⁵ due to trauma to the splenic vein. Besides, the anatomic arrangement of the pancreas into lobules precludes complete drainage unless each lobule be split. Operative handling of the pancreas serves no good purpose, but on the contrary, may destroy natural protective barriers.

2 *Lesser sac drainage* to prevent toxic product accumulation and forestall pseudocyst formation. Smead⁵¹ has demonstrated that the dilution and neutralization of these substances by blood and exudate is so complete that they are not harmful and removal is unnecessary.

3 *Cholecystostomy* to decompress the entire biliary tract. This procedure is less hazardous than common duct drainage with or without gallbladder excision. However, pancreatitis does recur after gallbladder drainage, as does the pre-existent cholecystitis. At times, emergency cholecystostomy must be done.

4 *Choledochostomy*, although more efficacious, can have no rational indication, except in the presence of jaundice due to stone, or dilated ductus choledochus.

5 *Cholecystectomy*, although it can accomplish the removal of the underlying cause, may add too much trauma to an already shocked patient. Too frequently have renewed attacks of acute pancreatitis followed immediately after this procedure, and too often have pancreatic pseudocysts resulted. Cholecystectomy is followed either by dilatation of the common duct with a continent sphincter of Oddi, or the sphincter too may dilate, with resultant incontinence. These events require time, and before such sphincter relaxation ensues, spasm may lead to pancreatic necrosis. Disturbed innervation results

in common duct and sphincter relaxation Unless this sphincteric atony occurs, increased biliary pressure results, and continues until either the ducts distend or the sphincter dilates This primary increase in pressure predisposes to acute pancreatitis Rost⁴⁸ reported a fatality in acute pancreatitis following instrumental dilatation of the sphincter at operation

Halstead,²⁸ in 1890, successfully operated on acute pancreatitis, merely establishing the diagnosis at celiotomy He closed the abdomen without drainage of the peritoneal cavity Halstead, again in 1901, unsuccessfully operated

TABLE IV—*Operative Findings in 154 Cases*

	Percentage
Fat necrosis	100%
Gall bladder disease	81
Calculi	54
Beef broth fluid	55
Granular omentum	29
Acute cholecystitis	23

upon Opie's case of stone impacted at the ampulla of Vater Von Haberer,²⁷ in 1909, advocated routine cholecystostomy to provide a drainage vent, but he presupposed ampullar block in all cases It thus becomes fairly well established that splitting the capsule and pancreatic drainage do not influence the pancreatic process for recovery and certainly in the severer cases, cholecystectomy and choledochostomy will not be tolerated

TABLE V—*Operative Procedures in 154 Cases With Mortality Rates*

	Cases	Deaths	Percentage
Cholecystectomy	30	2	6.6%
Cholecystostomy	83	20	24.0
Choledochostomy	2	0	0.0
Choledochostomy with cholecystectomy	10	0	0.0
Pancreatic drainage	23	14	60.8
Exploratory laparotomy	4	1	25.0
Incision and drainage of lesser sac	1	0	0.0
Multiple operations in the acute phase			
A—Pancreatic drainage followed by			
B—Cholecystostomy	1	0	0.0
Total	154	37	24.0

Korte,³² Abell,¹ Eggers,²⁰ Wolfer,⁵⁹ McWhorter³⁹ and Jones³⁰ have advocated immediate intervention Wangenstein,⁵⁶ Smead,⁵¹ Lewis,³⁴ Mikkelsen,³⁸ De Takats and MacKenzie⁵² indicated a preference for early conservatism followed by subsequent biliary tract operation

Ehason and North,²¹ although advocating early operation, conclude that emergency operation may not be best McWhorter,³⁹ who believes early operation the procedure of choice, observed the lowest mortality rates in the deferred operative group

Mortality rates of 50 per cent to 70 per cent are reported by many observers Mikkelsen³⁸ by delaying operative intervention from one to three weeks reduced his mortality to 7.5 per cent in 39 cases, 20 of whom were very ill Demel,¹⁶ from 1926 to 1934, operated upon 95 per cent of his 22 cases immediately, lost 78.3 per cent In the next 34 cases, but 50 per cent were operated upon immediately, with 26.4 per cent succumbing

During the past ten years, cholecystectomy has been our operation of choice, if performed one week to ten days after subsidence of acute symptomatology Ligation of the cystic duct, however, has been purposely omitted A soft rubber tube is placed over the cystic duct stump, thereby establishing a vent for biliary drainage should sphincteric spasm with possible recurrent acute pancreatitis ensue In effect, choledochostomy without its additional trauma and shock is accomplished, with decompression of the biliary system and concomitant removal of the focus of infection

Placing a drainage tube within the cystic duct would accomplish the same result, but with this difference if subsequent spasm did not occur, convalescence would be unduly delayed by persistent biliary drainage By placing the tube over the cystic duct, closure of this duct progresses without interference The danger of biliary peritonitis need give us no concern We have practiced this mode of treatment for the past ten years with happy results

Further analysis of the 154 cases will be found in the accompanying tables

SUMMARY

The pathogenesis of acute pancreatitis has been presented

Differential diagnosis has been discussed with especial emphasis on acute intestinal obstruction and perforated ulcer

The immediate operative and conservative forms of therapy have been compared

Our present mode of delayed operation has been described

There remains but one further thought, and that is to urge the necessity for removing the principal offending organ before the complication of recurrent acute pancreatitis presents itself

The authors wish to thank those surgeons whose cases were used in the preparation of this paper

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INTRATHORACIC PHEOCHROMOCYTOMA WITH HYPERTENSION*

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A PHEOCHROMOCYTOMA usually occurs in or near the adrenal glands but may occasionally be found in other parts of the chromaffin system. The tumor derives its name from the fact that the cytoplasm of the component cells contains a reddish-brown pigment when the tissue is fixed in chromate solution. These characteristic cells may produce epinephrine and thus cause paroxysmal or persistent hypertension. A case of intrathoracic pheochromocytoma with hypertension in which the tumor was successfully removed by operation is presented in this paper. The extra-adrenal pheochromocytomas reported in the literature are briefly analyzed.

Although only a very small percentage of cases of high blood pressure are caused by an adrenalin-producing tumor of the chromaffin system, this lesion should always be considered in the differential diagnosis of hypertension. The blood pressure elevations caused by a pheochromocytoma are not necessarily of a paroxysmal type. In some cases, especially those of long standing, there is persistent hypertension with little fluctuation. According to Green's review⁸ of 51 cases of pheochromocytoma with hypertension, only 14 had a normal blood pressure between paroxysmal elevations, while the other 37 patients constantly showed some elevation of blood pressure. Since the pheochromocytoma was removed surgically in 12 of the 14 cases which had a normal blood pressure between the hypertensive paroxysms, it can only be conjectured whether these patients, if untreated, would have eventually developed sustained elevations in blood pressure as has been suggested by Wells and Boman.²⁵ Some pheochromocytomas apparently produce no adrenalin and therefore do not cause hypertension.

According to Kohn¹¹ chromaffin cells can be found along the entire length of the autonomic nervous system, and occur in nests in the autonomic ganglia. Some authors employ the term "paraganglioma" for the extra-adrenal chromaffin tumors arising in the paraganglia. Most of the extra-adrenal pheochromocytomas that have been reported have been found in retroperitoneal portions of the abdomen, usually near the kidneys or in the aortic bodies or organs of Zuckerkandl which are located on either side of the aorta at the origin of the inferior mesenteric artery. Although the carotid body is a part of the chromaffin system, no adrenalin-producing tumor in this region is on record. However, a case of carotid body tumor, which contained no pressor substance, and concurrent pheochromocytomas of both Zuckerkandl bodies has been reported.³

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Intrathoracic pheochromocytomas are extremely rare. To date, only two such tumors, diagnosed at autopsy, have been reported. Only one of these was known to have caused hypertension. The case reported here is apparently the first in which a diagnosis of intrathoracic pheochromocytoma with hypertension was made during life. The true nature of the lesion was suspected prior to operation because this young man had both an unexplained hypertension and an intrathoracic tumor in the region of the sympathetic chain in the costovertebral area.

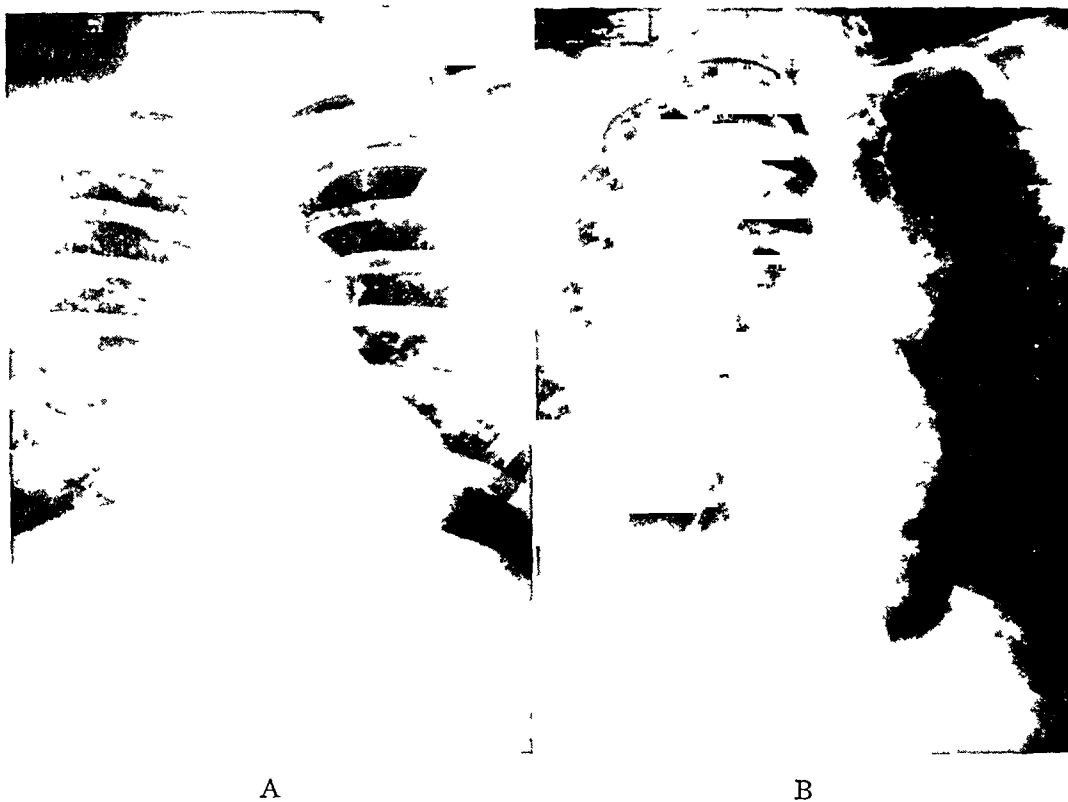


FIG 1—A Posteroanterior roentgenogram of chest shows a small rounded mass projecting from the mediastinal shadows just below the arch of the aorta

B Oblique view shows mass in left costovertebral region extending from the fifth to the seventh ribs

CASE REPORT

V K, male, age 25 years, entered the army when he was 22 years old and at that time he had a normal blood pressure. Later, while in service, hypertension was discovered. During the course of a diagnostic study, a roentgenogram of the chest revealed a small tumor mass in the left costovertebral area just below the level of the arch of the aorta. Re-examination of the induction film showed that the shadow had been present at that time. After a thorough investigation, a diagnosis of essential hypertension and neurofibroma of the costovertebral area was made. The patient complained of easy fatigue, increasing nervousness, palpitation, slight dyspnea, occasional dizziness, headaches and sweating of the hands. No pulmonary symptoms were present. Physical examination revealed a well developed and well nourished male. There was considerable moisture of the palms of the hands. The systolic blood pressure varied between 190 and 210 mm Hg.

INTRATHORACIC PHEOCHROMOCYTOMA

and the diastolic pressure between 100 and 120 mm Hg. The physical examination was otherwise negative. Roentgen studies at this time (Fig 1) revealed that no appreciable change in the size of the mass had occurred in a two and a half year period.

Operation was performed on November 2, 1945, under ether-oxygen intratracheal anesthesia. Because an intrathoracic pheochromocytoma was suspected, blood pressure readings were taken every five minutes during the operation, and adrenalin was ready for immediate injection. Through a posterolateral transpleural incision on the left side, the tumor was exposed. A purplish-red mass measuring 5 by 4 by 5 cm was found in the



FIG 2—Photomicrograph of pheochromocytoma. The characteristic arrangement of tumor cells in lobules separated by capillaries is shown ($\times 150$). Insert shows chromaffin granules ($\times 640$).

costovertebral area just lateral to the upper portion of the descending aorta. The mass rested on the ribs and intercostal structures in the costovertebral groove. It was covered by pleura, was fairly well encapsulated and was soft in consistency. The sympathetic nerve trunk traversed the mass. The appearance and consistency of the tumor was more that of a glandular structure than that of a neurofibroma. Care was taken to minimize manipulation of the tumor during the freeing of the mass in order to avoid a hypertensive crisis. Within five minutes of clamping the blood vessels leading to the tumor, the systolic blood pressure dropped from 220 to 110 mm Hg and a few minutes later was barely obtainable. Intravenous adrenalin was given and a gradual elevation of the blood pressure occurred. Aside from the dramatic change in blood pressure, the patient's condition appeared satisfactory. The blood pressure was within a normal range throughout

the first postoperative day, but on the second day the systolic pressure rose to about 160 mm Hg where it remained. The postoperative course was otherwise uneventful.

The pathologic specimen consisted of an oval mass of tissue weighing 28 Gm. The surface was deep red and one portion was covered by a grayish-white membrane. Microscopic examination revealed a neoplasm which was made up of small or medium sized nests of tumor cells separated from each other by a relatively scanty stroma rich in congested capillaries. The tumor cells were medium sized and oval, polyhedral or irregular in shape, with a fair amount of pale staining vacuolated or finely granular cytoplasm and eccentrically placed, generally round, compact nuclei. Several syncytial masses, resembling irregular giant cells were observed. A few mitotic figures were noted. The tumor was fairly well circumscribed by a capsulelike layer of connective tissue. It presented many small areas of hemorrhage and here and there were clumps of brown pigment. The pathologic diagnosis was pheochromocytoma (Fig. 2).

Because the blood pressure was still somewhat elevated, perirenal air studies were done by Dr. George Cahill in March, 1946, but no evidence of a tumor in the adrenal region was found. The patient also had a test performed with a benzodioxan derivative.⁶ A drop in the blood pressure upon the injection of this adrenaltic substance is known to occur in cases of pheochromocytoma. No change in blood pressure was recorded in this patient. The test suggested that no further adrenaline-producing tumor tissue remained.

During the first two years following operation the blood pressure ranged between 160 to 180 systolic and 100 to 110 diastolic. The feeling of weakness and the other symptoms which were present prior to operation disappeared although some nervousness remained. Two and a half years after operation the blood pressure was 140/80 mm Hg. The patient was feeling well and leading a normal active life three years postoperatively.

DISCUSSION

In about 12 per cent of the cases of pheochromocytoma recorded in the literature, the tumor was located outside of the adrenal area. An analysis of these 19 cases of extra-adrenal pheochromocytoma^{1, 5, 7, 9, 10, 12-14, 16, 21, 23} reveals that the sex distribution is approximately equal. Although the age of the patients varied widely, over one half were less than 40 years old. The tumor may occur in childhood. In several instances an operation had been undertaken because of the presence of an abdominal mass, but a correct preoperative diagnosis was rarely made. In over one half of the recorded cases the tumor was an unexpected finding at autopsy. In some instances the cause of death was unrelated to the tumor, but in several cases signs of arteriosclerosis were present at postmortem examination. This finding is significant as the majority of these patients were under 40 years of age. Hypertension was known to have been present in a few cases, but most of the reports of extra-adrenal pheochromocytomas either deny hypertension or fail to record the blood pressure. One patient, admitted to the hospital in a critical condition, showed a hypotension until death a few days later, autopsy in that case revealed a hemorrhage into a retroperitoneal pheochromocytoma.⁵

The first intrathoracic pheochromocytoma, an incidental finding at autopsy in a 39-year-old female, was reported by Miller¹⁷ in 1924. The tumor was in the right costovertebral area at the level of the sixth rib, and was about the size of two walnuts. The report did not state whether the patient had had hypertension.

The second intrathoracic pheochromocytoma diagnosed at autopsy was reported by Philips¹⁹ in 1940. This man was 39 years old at the time of death, but was known to have had hypertension since the age of 29 years. He complained of episodes of cardiac palpitation and throbbing in his head, as well as some dyspnea, polyuria and nocturia. At 33 years of age he experienced a left hemiplegia. The heart was enlarged and the blood pressure varied between 170 mm Hg and 220 mm Hg systolic, while the diastolic pressure was about 120 mm Hg. Roentgenographic examination of the chest showed a mass at the left apex posteriorly, which did not move on swallowing and did not compress the trachea. The patient also had a Horner's syndrome on the left side. Six years later the patient had an acute coronary occlusion and died in congestive heart failure. At autopsy a firm mass about the size of a plum was found at the apex of the left pleural cavity. The mass was not attached to the lung and was easily shelled out. In addition to the tumor, the autopsy revealed myocardial infarction and marked arteriosclerosis of the coronary arteries, aorta and renal vessels.

Wahl and Robinson²⁴ reported a case of neuroblastoma of the mediastinum with pheochromoblastomatous elements. The patient, a four-year-old boy, died of a neuroblastoma in the upper posterior thoracic region which had metastasized diffusely. Microscopic examination of the primary tumor revealed a sympathogonioma with mixed neuroblastic and pheochromoblastic elements. Transition could be seen between primitive nerve cells and the chromaffin cells. The metastases were all of the embryonic neuroblastomatous type whereas the differentiated elements were present only in the primary growth. The child's blood pressure was not mentioned.

Pheochromocytomas may be multiple. In approximately 15 per cent of adrenal pheochromocytomas the tumor is bilateral. Occasionally one tumor may be in the adrenal region and a second one in the organs of Zuckerkandl or in some other retroperitoneal region. The number of extra-adrenal pheochromocytomas that have been reported are too small to justify an opinion as to whether or not the likelihood of multiple pheochromocytomas is greater when one of the tumors is located outside the adrenal region. It is only during the past few years that cases with coexisting intra-adrenal and extra-adrenal pheochromocytomas have been cured by surgical excision. The two previously reported intrathoracic pheochromocytomas were solitary tumors found at autopsy. In my patient the persistence of some hypertension for a considerable time postoperatively raised the question at that time whether another pheochromocytoma might be present, but laboratory tests and the later clinical course did not support this supposition.

The association of pheochromocytomas and neurofibromatosis is significant.²² When both types of tumors are present, the pheochromocytoma might clinically be mistaken for another neurofibroma.

A small number of malignant pheochromocytomas have been reported. Apparently hypertension has not been present in the malignant cases. This is

not surprising when one bears in mind the fact that the production of adrenaline requires a marked degree of cell differentiation and cancer is more frequently found in undifferentiated cells. The cases of malignant pheochromocytomas have shown bilateral adrenal involvement. The metastases may be widespread.

The symptoms presented by some patients with a pheochromocytoma can easily be confused with hyperthyroidism. Nervousness, sweating, intolerance of heat, weight loss in spite of good appetite, easy fatigue and palpitations may be present. In some such cases of pheochromocytoma the basal metabolic rate may be considerably elevated due to hypermetabolism.¹⁵

Surgical removal of a pheochromocytoma usually causes the blood pressure to return to normal levels. This correction of hypertension may even occur in some cases with preoperative disturbance in renal function and hypertensive retinitis, but it must be assumed that in some advanced cases the changes will be irreversible.

Since the hypertension in cases of pheochromocytoma is due to circulating epinephrine, adrenolytic drugs have been studied as a test for this lesion. Goldenberg *et al*⁶ report that some benzodioxanes injected intravenously cause a transient drop in blood pressure in patients with hypertension produced by a pheochromocytoma, whereas no drop in blood pressure occurs when a similar test is applied to other cases of hypertension.

CONCLUSIONS

The diagnosis of intrathoracic pheochromocytoma should be considered when a tumor in the costovertebral portion of the chest is associated with paroxysmal or sustained hypertension, especially in the younger age group. Roentgenograms of the chest are indicated in all patients with symptoms and signs suggestive of excess circulating epinephrine. Pheochromocytoma is added to the list of intrathoracic tumors requiring surgical excision.

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SPONTANEOUS RUPTURE OF THE ESOPHAGUS

REPORT OF TWO CASES ONE WITH RECOVERY AFTER SURGICAL REPAIR*

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SPONTANEOUS RUPTURE of the esophagus is a rare, and from previous reports apparently a universally fatal accident. Excellent reviews have been furnished by Fitz,⁹ Walker,²³ Klein and Grossmann¹⁶ and more recently by Eliason and Welty⁸ and Barrett.^{2A} In 1946, Eliason and Welty⁸ stated that 41 cases had been recorded. They added three more cases, the mortality of the 44 cases being 100 per cent.

Since their report, at least ten^{2A, 10, 15, 20, 24} additional proved fatal cases have been recorded, making a total of 54 cases with a 100 per cent mortality. The ten recent cases will be reviewed briefly.

In 1946, Barrett^{2A} reported three cases of spontaneous perforation, one of which was proved to be a rupture. The patient, a 45-year-old male, had sudden onset of back pain after a short prodromal period of malaise, and collapse developed rapidly. Because of predominantly abdominal signs, a diagnosis of perforated ulcer was made and abdominal exploration performed. He succumbed 24 hours after operation and 26 hours after the onset of the acute illness. At postmortem, the esophageal rent was $\frac{1}{2}$ inch long and was located $2\frac{1}{2}$ inches above the diaphragm.

Foggitt¹⁰ reported the case of a 55-year-old woman in whom the diagnosis was made preoperatively by a barium swallow. The rent in the esophagus was repaired by the abdominal approach, with death resulting two days after admission.

Weder,²⁴ in 1943, reported a case of rupture which might not be considered truly spontaneous since the patient was known to have a stricture, and the rupture followed forced swallowing of a large piece of meat impacted in the stricture. However, the rupture occurred in the normal esophagus well below the stricture. The patient died 46 hours after the rupture despite drainage of the neck and pleural cavity. The esophageal rent at postmortem was 6 cm long.

Pembleton²⁰ in 1947 reported briefly a case of esophageal rupture secondary to indirect trauma, when a weapons carrier fell over on the patient, a soldier. This patient had a severe tension pneumothorax, due to the ruptured esophagus which was the cause of death nine hours after injury.

Other cases previously recorded, secondary to trauma, were those of Aldrich and Anspach,¹ Griffith¹³ and Murdoch.¹⁹

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McLeod and Gardner¹⁷ reported the case of a 58-year-old male who had been on an ulcer regimen for gastric ulcer. He suddenly developed epigastric pain with vomiting and rapid onset of shock. With the diagnosis of perforated ulcer, an abdominal exploration was carried out. No intra-abdominal lesion was found and he succumbed 25 hours after the onset. At postmortem examination 1800 cc of coffee ground material were found in the left pleural cavity with a longitudinal rent 3.5 cm long on the postero-lateral wall of the esophagus.

Most recently, Kinsella *et al*¹⁵ reported five cases with a mortality of 100 per cent, although one death cannot be ascribed to the disease itself.

Perforation, as distinguished from rupture of the esophagus, is more common, especially that secondary to foreign body, stricture or instrumentation. Reported cures of these cases are not uncommon. Even cases of perforated peptic ulcer of the esophagus, which may at times be painless and so seemingly spontaneous, are not so rare, and at least one such case has been cured by pleural drainage (Benson and Penberthy³). Barrett^{2A} in his excellent review included cases of both spontaneous rupture and perforation.

Several cases of spontaneous perforation have been reported recently, including those of Casper⁴ and Culver and Clark.⁶ Several cases in which it is difficult to determine the exact pathology, whether perforation or rupture, have been reported. These have been cases which have survived for a long time on conservative treatment and then have had pleural drainage with the diagnosis being made by passage of swallowed fluid or food. The patients of Frink¹¹ and Moore and Murphy,¹⁸ both of whom recovered, fall into this category. A similar case, seen in this hospital, is being reported in detail by Dr Paul Vestal. Still another case was recorded briefly in a general discussion by Cummings.⁷

Of the 54 cases of proved spontaneous rupture reviewed, eight^{5, 8, 10, 12, 15, 21, 23} were diagnosed preoperatively or premortem and only three received definitive surgical treatment,^{5, 10, 15} the third being Case 5 of Kinsella *et al*. Many cases, of course, were seen before the day of thoracic surgery. The first case to be diagnosed and treated surgically was that of Collis *et al*.⁵ Their case was diagnosed by the presence of subcutaneous emphysema in the neck and confirmed by barium swallow. Exploration was carried out through the chest and the esophageal rent was closed, but the patient unfortunately succumbed.

Foggitt¹⁰ explored the distal esophagus through the abdomen after making the diagnosis in a similar manner. The rent was closed after pulling the esophagus down into the abdomen. A gastrostomy was made at the same time, but despite this the patient succumbed 48 hours after the onset.

Kinsella¹⁵ made the diagnosis in Case 5 of their group of cases, this was confirmed by barium swallow, and eight and one-half hours after the rupture, operation was performed. The patient was doing well on the eighth postoperative day when he succumbed to a pulmonary embolus.

More recently a case of perforation of the esophagus has been treated surgically by Barrett^{2b} with survival. The patient, a female, was explored through the chest seven hours after the onset which occurred in the late convalescence from a pelvic operation. A tiny perforation was found 1½ cm above the diaphragm, closed with a purse string suture and the area drained. A leak developed on the eighth day, and was followed by formation of a mediastinal abscess, which required drainage. A lung abscess developed in the R U L which drained spontaneously through the bronchus. Three months after the operation the patient was well.

Two cases treated at New Haven Hospital are the subject of this report: the first, a case of rupture diagnosed and treated successfully by surgery; the second, a fatal case of rupture diagnosed incorrectly. A third case, diagnosed as spontaneous perforation of the esophagus and treated by laparotomy with survival after late diagnosis and thoracotomy drainage, is being reported in detail by Dr. Vestal. Only Case No. 1 was seen by the author.

Case 1 W S, N H H No B34078, a male Negro of 35 years, was admitted to the Emergency Room of N H H at 6:30 A M, August 9, 1948, complaining of severe high epigastric and substernal pain. The diagnosis of the admitting intern was renal calculus or perforated duodenal ulcer. Roentgenograms of the abdomen revealed no gross abnormalities. The patient was then seen by the surgical resident on call (Dr. Kremenetz) who noted subcutaneous emphysema in the neck and made a tentative diagnosis of perforated ulcer of the esophagus.

At 3:00 A M the patient had been awakened by substernal and epigastric discomfort with a sense of fullness and a great thirst. He rose, obtained ice water and drank three glasses very quickly. Following this, he was seized by agonizing substernal and epigastric pain. Almost immediately he became nauseated, retched and vomited a "cup full" of bright red blood. The pain, nausea, retching and vomiting persisted. Within about an hour, the pain radiated around the costal margin and then up to the left shoulder. About the same time he noted respiratory difficulty with pleuritic pain. He then was brought to the hospital.

The past history was obtained piece-meal, with some discrepancies. The patient stated that he had had for over ten years rare attacks of epigastric fullness with substernal discomfort. These attacks were always relieved by taking water, or food. There was some question of his having had tarry stools immediately before the onset of the present illness. Although the patient denied it on admission, the history was eventually obtained that he had been on an alcoholic spree the weekend before the onset of the present illness.

Examination revealed a well-developed and extremely apprehensive Negro obviously in acute distress, with pulse ranging from 100 to 140, respirations 40, temperature 101° and B P 110/70. There was easily palpable subcutaneous emphysema in the neck. The respirations were very shallow and the patient could not be persuaded to take deep breaths. There were no changes in percussion noted but definite diminution of breath sounds particularly over the lower left chest. The abdomen was rounded and there was tenderness, moderate spasm and rebound tenderness over the epigastrium. The remainder of the examination was unremarkable. Laboratory studies: RBC 3,070,000, WBC 11,500 with 90 per cent polys, Urine 7-15 WBC, Plasma protein 5.95, Chlorides 111.6, NPN 29.

Roentgenograms of the chest revealed mediastinal emphysema on the left and interstitial emphysema in the neck plus a questionable small pleural effusion on the left. A lipiodol contrast study of the esophagus, using 15 cc, revealed a normal esophageal pat-

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tern, but with an extravasation of a large quantity (about $1/3$ of the dye) into the mediastinal soft tissues to the left and posteriorly (Fig 1)

The patient was given penicillin, intravenous sodium sulphadiazine and infusions. His pain persisted with slight relief from morphine, and he developed clinical signs of fluid in the left pleural cavity and increasing signs of peritoneal irritation. It was decided that the best chance of cure was with operation. A Levine tube was passed into the stomach with ease. At 12 00 noon he was taken to the operating room at which time his pulse was 140, respirations 40 and blood pressure 97/40. Endotracheal anesthesia followed sodium pentothal induction, supplemented by cyclopropane and ether with a small amount of curare.



FIG 1

FIG 1—(Case 1) Oblique view after swallow of lipiodol to show extravasation of opaque medium into mediastinum

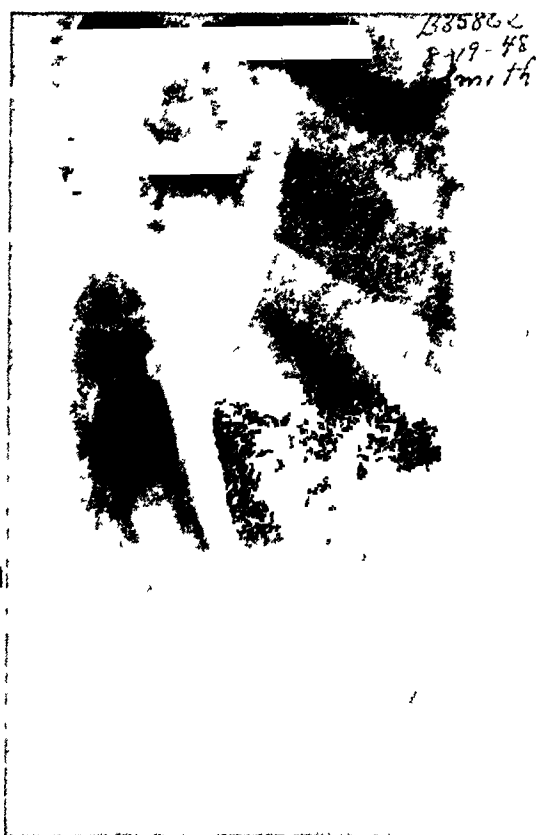


FIG 2

FIG 2—(Case 1) Lateral view after barium swallow on the tenth p.o. day. Note the narrowing without obstruction. The AP view could not be reproduced satisfactorily.

The left thoracic cavity was entered through the bed of the ninth rib. The pleura was seen to be inflamed and the pleural cavity contained a quantity of dirty, dark gray-yellow material which had the typical appearance of gastric juice containing blood. As the lung collapsed, the lower lobe was found to be fixed to the mediastinum by fresh fibrinous adhesions. As this membrane was peeled off it was seen to be superficially necrotic in an area about 3 to 4 cm. in diameter. The lower mediastinum and the tip of the pulmonary ligament were necrotic and perforated. Dirty fluid exuded through the openings.

A cavity in the mediastinum about 5 by 3 by 2 cm was entered through the necrotic mediastinal pleura. A brief attempt was made to visualize the esophagus in this area and then the diaphragm was opened and the fundus of the stomach and the abdominal esophagus were picked up and delivered into the chest. There was no evidence of perforation into the peritoneal cavity, but as the esophagus was freed in the esophageal hiatus, the necrotic reaction was seen to extend to the peritoneal side of the diaphragm. At a point

approximately 1 cm above the diaphragm, the lower end of a tear in the esophagus was seen. The longitudinal tear on the left posterolateral surface of the esophagus was over 4 cm in length. The stomach tube lay against the opposite wall. Although a resection had been planned, a local repair appeared feasible at this time, so a three layer closure was performed. The first layer consisted of a running suture of 00 chromic intestinal catgut in the mucosa alone, the second of the same type suture through all layers and the third an inverting layer of Halsted silk mattress sutures in the muscularis. The mediastinum, especially in the necrotic area, was carefully irrigated and the organs were returned to their normal positions except for a long, thin tongue of omentum which was fixed upon the suture line. The diaphragm was then closed. The mediastinum was left open up to the root of the lung and the superior mediastinum was also incised, albeit with some difficulty because of the low incision. Chest closure was with three suction catheters, one posteriorly lying on the diaphragm with its tip very close to the mediastinum, one anterolaterally just lateral to the pericardium, and one anteriorly in the third interspace. One hundred thousand units of penicillin were sprayed over the mediastinal area.

The patient's immediate postoperative course was satisfactory, with relief of his pain, but with elevation of pulse, temperature and respirations. However, on the third postoperative day he rapidly developed a severe delirium reminiscent of delirium tremens and his course for the following few days was stormy. Delirium was controlled by paraldehyde and supportive measures including large doses of vitamins.

On the sixth postoperative day a friction rub was noted over the right lower chest,

with effusion developing subsequently as shown by physical examination and roentgen ray. On the seventh postoperative day he showed evidences of thrombophlebitis of both lower extremities, but there were no further complications. The anterior drainage tube was removed on the seventh postoperative day, the antero-lateral tube on the twelfth postoperative day and the posterior tube on the sixteenth postoperative day. He was started on fluids by mouth as soon as his serious delirium permitted, on the seventh postoperative day. Roentgenogram of the esophagus on the tenth postoperative day showed narrowing of the esophagus on the lateral projection (Fig 2) and minimal narrowing on the AP



FIG 3—(Case 1) AP view after barium swallow four months after operation. Outlined in dotted lines because of poor contrast. No narrowing or obstruction present.

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projection Repeat barium swallow on the twenty-second postoperative day revealed only minimal narrowing A right thoracentesis was done on the twenty-third postoperative day and 50 cc of fluid obtained, culture of which was negative A gastric analysis on the twenty-sixth postoperative day revealed a fasting free acid of 20 units He was discharged well on the twenty-seventh postoperative day, taking a full gastric diet without difficulty

Additional note, May 8, 1949 Case 1 has been followed until this date and the patient has been eating a regular diet without any difficulty Roentgenograms of the esophagus on Dec 15, 1948, revealed no narrowing (Fig 3)

Comment. This case showed the typical symptoms and signs of esophageal rupture Despite this, the impressions of the first observers were of an intra-abdominal lesion rather than the correct diagnosis When suspected, the diagnosis was quickly confirmed

Case 2 J R, N H H No 74073 This 75-year-old white male was admitted to N H H Emergency Room at 7 45 P M on January 27, 1947, complaining of severe pain in the left side and the epigastrium

The onset had been sudden at 10 35 A M, approximately ten hours before admission, when he became nauseated and vomited while walking up stairs Following this, there was no further vomiting but the severe pain persisted, despite small amounts of water and soda taken by mouth

On admission he was evidently desperately ill, with pulse 100, blood pressure 100/70, respirations 30 and temperature 101 8° There was splinting of the left chest with signs of fluid up to the level of the seventh dorsal spine The abdomen showed slight distention with moderate tenderness in the epigastrium and l u q There was evident cyanosis, and the extremities were cold

The past history revealed previous admissions over a period of years to clinic and hospital for lues, nerve deafness, arterio-sclerotic heart disease and a ruptured appendix six months before this admission

The WBC was 4,700, with 76 per cent polys Urine examination revealed one plus albumin and two plus sugar without acetone

The clinical diagnosis entertained by the medical staff in order given were (1) acute pancreatitis, (2) coronary occlusion, (3) incarcerated diaphragmatic hernia, (4) perforated stomach or duodenum, (5) subdiaphragmatic abscess and (6) hydronephrosis with pyelonephritis

Roentgen ray showed a pleural effusion with pneumonitis on the left, dilatation of the large bowel with the question of a subdiaphragmatic mass on the left He was treated with infusions and penicillin His blood pressure fell rapidly and he died in collapse at 8 00 A M, about 21½ hours after onset of his present illness Just before death, a thoracentesis obtained foul brown fluid Culture revealed mixed organisms

At postmortem 1800 cc of foul chocolate colored fluid were found in the left pleural cavity with complete collapse of the lung The lower mediastinum was distended slightly to a point above the aortic arch with the same type of fluid There was an opening 4 mm in diameter from the mediastinum to the pleural cavity Pressure on the stomach forced more fluid through this opening There was a small pericardial effusion (30 cc) On exposure of the lower esophagus, a 3 cm longitudinal tear was seen on the anterior surface, with its lower edge at the esophageal hiatus The edges were ragged and stained dirty brown The edges of the mucosal tear, which was 6 cm long, were sharp as if it were split by a scissors The wall of the stomach and esophagus in this region were soft and unchanged except for slight edema Microscopic examination showed plasma cells tightly packed in the mucosa, with some fibrosis of the deeper layers of the mucosa and submucosa

Comment This case history again is typical, and the course much more typical of rupture of the esophagus than that in Case 1. The diagnoses considered are those which have been made most frequently in previously reported cases. No mention was made of interstitial emphysema of the neck, but it may have been missed as by the first three observers of our Case 1. The roentgenogram showed a large bubble of air in the lower mediastinum which should have aroused suspicion of the esophageal rupture. The diagnosis could have been confirmed by the aspiration of a large quantity of foul fluid of the usual color from the pleura.

DISCUSSION

As shown by these two cases and outlined by previous authors, proper treatment of this condition depends on early diagnosis, for in most instances the course is rapidly down-hill with early development of shock, collapse and death. In many cases, death occurs within 24 hours and in the majority within 48 hours. Only 15 per cent survived more than 48 hours. This very rapid course may possibly be altered by modern chemotherapy and supportive measures, although this was not so in our Case 2 or in the more recent cases outlined above.

If rupture of the esophagus is kept in mind, the diagnosis should be entertained because of the distinctive symptomatology and then confirmed by the characteristic physical and roentgen ray findings. The patient is usually a male (five to one) who may or may not complain of previous epigastric or substernal discomfort. After a bout of drinking or other overindulgence, he suffers an attack of violent vomiting almost always with blood present, followed by severe high epigastric or substernal pain. Occasionally the pain first occurs in the back or is referred there early in the course. Referral of pain to the costal margin or to the left shoulder and pleuritic pain are frequent. A characteristic of the pain is its constancy. With or without signs of pleural involvement, limitation of respiration is usually a leading complaint.

The most valuable clinical sign for diagnostic purposes and the one most commonly present is cervical interstitial emphysema in the presence of low substernal or epigastric pain. In many cases there will be signs of pneumothorax, hydrothorax or both. The standard roentgenogram of the chest may show mediastinal gas shadows, sometimes with fluid levels. A definite diagnosis may be made by the demonstration that a swallow of lipiodol extravasates into the mediastinum or pleural cavity.

The erroneous diagnoses most frequently made in these cases include coronary occlusion, pulmonary embolus, dissecting aneurysm, perforated ulcer of the stomach or duodenum, acute pancreatitis and renal colic. As indicated in the case reports, perforated ulcer and renal colic were first considered in Case 1 and a melange of diagnoses were considered in Case 2. The diagnosis of an intraperitoneal surgical accident has been so strongly suspected in these cases that laparotomy has been carried out all too frequently.^{1 2A 8, 14, 15, 17 18,}

Once the diagnosis of spontaneous rupture of the esophagus has been made, the treatment is surgical. Despite the shock-like picture, this must be performed early, combined with supportive measures. The experience with good, conservative treatment has been universally poor with a reported mortality of 100 per cent. In cases of perforation the need for surgery is not so urgent, as their course is less precipitously downhill. Even these cases, when treated conservatively, have a very stormy course, and their course undoubtedly would be shortened and the mortality decreased by early definitive surgery.

SUMMARY

A brief review of the previous experience with spontaneous rupture of the esophagus, its symptomatology and differential diagnosis have been given. Two cases of spontaneous rupture, one of which recovered as a result of early diagnosis and surgical treatment, have been reported.

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GASTROPERICARDIAL FISTULA FOLLOWING TRANSTHORACIC ESOPHAGECTOMY*

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The transthoracic approach to cancer of the esophagus and cardia is now well established. In the interest of collecting all possible data relative to this operation we present the first reported case of gastropericardial fistula occurring as the remote terminal complication in a case of transthoracic esophagectomy with esophagogastrostomy.

Case Report In March, 1946, a 54-year-old white man was admitted to Cleveland City Hospital complaining of progressive dysphagia of 5 months' duration. Physical examination, blood count and blood chemistry showed no abnormalities. Radiograph of the chest was normal. Fluoroscopic and film studies of the esophagus and upper gastrointestinal tract showed an irregular constricting filling defect of the lower third of the esophagus with dilatation of the esophagus above the site of stricture. Esophagoscopy revealed an area of constriction but no definite tumor. Biopsy of the esophageal wall about the site of the stricture was reported as adenocarcinoma. On March 18, 1946, a transthoracic resection of the lower third of the esophagus and upper stomach was carried out with esophagogastrostomy. At operation there were no palpable lymph nodes in the mediastinum or hilum of the left lung and the procedure was carried out without incident. The pathologic diagnosis was partially differentiated adenocarcinoma of gastroesophageal junction consistent with carcinoma arising from gastric mucosa. The postoperative course was uneventful and the patient was discharged on the seventeenth postoperative day.

On October 14, 1946, he returned to the outpatient department complaining of substernal pain and dysphagia relieved by alkali. Esophagoscopy revealed an easily dilatable soft stricture 30 cm from the incisor teeth (the stomal level) with an area of ulceration on the posterior wall of the stomach just beyond the stoma. Several biopsy specimens were taken about the stoma both proximally and distally. These sections were reported as showing papillomatous overgrowth of the squamous epithelium of the esophagus with adjacent ulcer formation, a silk suture was found in the sectioned material. Fluoroscopy and barium studies showed a patent gastroesophageal anastomosis which permitted barium to rush through easily. There was some evidence of gastric retention but no indication of recurrent tumor. The stoma was progressively and repeatedly dilated to No 34. The patient was treated with antispasmodics and a bland diet regimen for the marginal ulcer, with fairly good clinical response.

Esophagoscopy in June, 1947, revealed a tumorous stricture of the anastomosis, biopsy of this area was reported as adenocarcinoma. Roentgen study (Fig 1) at this time showed a constant fixed constriction of the distal esophagus with irregular filling defects in its borders. Radiograph of the chest showed a left pleural effusion and haziness of the left cardiac border with a double contour suggesting pericardial effusion. These findings probably represented the early manifestation of pericardial invasion by the recurrent tumor.

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The patient's final admission was in September, 1947, for increasing dysphagia, dyspnea, and persistent, boring left-sided chest pain. Examination now revealed a pale debilitated man with left pleural effusion, a liver that was palpably enlarged 6 cm below the costal margin, and dilated superficial abdominal veins. Thoracentesis yielded 450 cc of serosanguineous fluid which contained no tumor cells on microscopic cell block. On September 27, 1947, a Witzel gastrostomy was performed as a palliative feeding procedure. The postoperative course was characterized by fever, leukocytosis and progressively increasing dyspnea. Examination now revealed peculiar splashing and clicking



FIG 1—Examination in July, 1947, demonstrates an irregular, constant rigid, constriction of the distal 2 to 3 cm of the esophagus with irregular defects in the mucosa at the esophagogastric junction, indicating recurrence of the carcinoma.

sounds in the heart cycle associated with distention of the neck veins and a venous pressure of 28 cm of water. The electrocardiogram was typical of pericarditis. Chest radiographs (Figs 2 and 3) showed a hydropneumopericardium. Aspiration of the pericardium was easily performed and the fluid and air were obtained very freely. The fluid was deep yellow with a specific gravity of 1.017, pH of 6.0 and showed yeast cells on smear. Pericardial aspiration offered the patient transitory relief of dyspnea but a film taken immediately following aspiration showed no change in the cardiac silhouette. Methylene blue swallowed by the patient could be aspirated from the pericardium. Repeated pericardial paracentesis and oxygen failed to relieve the cardiac tamponade and pericardiostomy was done on October 8, 1947, for decompression. The patient expired 36 hours after the procedure.

Autopsy The most striking findings were in the chest. Both pleural spaces were partially obliterated by fibrous adhesions and there were 350 cc of clear yellow fluid in the left pleural space and 200 cc in the right. The left lung was firmly adherent to the pericardium, lateral mediastinum and posterior chest wall. The pleural surfaces of the left lung were markedly thickened. Sections showed the pleural thickening to be made up of partially differentiated adenocarcinoma. There was atelectasis of both lower lobes of the lungs. The walls of the pericardial sac measured up to 0.4 cm in thickness and its inner surface was shaggy and dull gray. Histologic examination showed acute and chronic pericarditis with fibrin de-

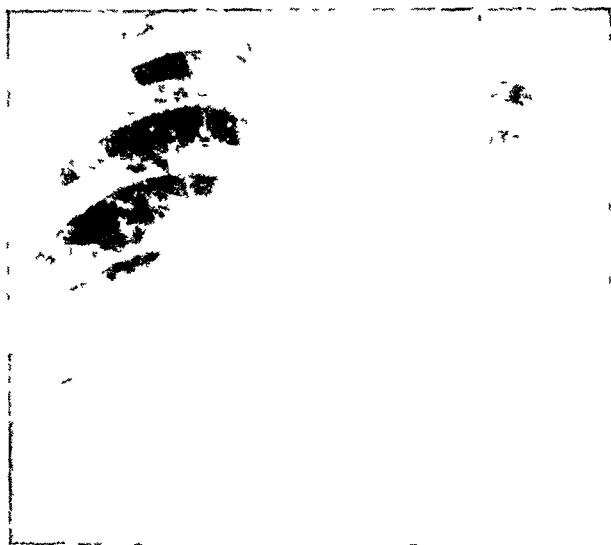


FIG 2



FIG 3

FIGS 2 and 3—Radiographs of the chest show marked enlargement of the cardiac silhouette with thickening of the parietal pericardium most marked on the right. In the pericardial sac there is air and fluid and two large fluid levels indicating hydropneumopericardium. The left costophrenic sinus is obscured and there is a left pleural effusion.

position. The pericardiostomy was represented by a defect in the anterior pericardial wall which measured 6 by 4 cm and was continuous with the subcutaneous tissue of the right chest. In the posterior wall of the pericardium there was a large defect measuring up to 5 cm in diameter through which the mucosal surface of the posterior wall of the stomach was seen (Figs 4 and 5). The edges of this defect were composed of firm grayish white tissue and measured up to 0.8 cm in thickness. Sections showed tumor tissue similar to that found at operation. This invaded all layers of the stomach wall and could be seen extending down into the pericardial wall. The inner lining of the pericardium blended with the submucosal of the underlying anterior stomach wall. The heart was enlarged in all diameters and weighed 525 Gm. Its epicardial surface was shaggy and gray and there was a recent laceration of the subepicardial fat which had been caused by the pericardial aspiration. There was no free fluid in the pericardial cavity. The site of the previous gastro-esophageal anastomosis was posterior to the pericardium. The distal 2 cm of the esophagus was thickened and the walls were firm and grayish white. The lumen at this point was narrowed and measured 0.8 cm in

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diameter Sections demonstrated the presence of tumor in the thickened portions of the esophagus This was similar to that removed at the time of operation The anterior surface of the esophagus and stomach were attached to the posterior pericardium and left lateral mediastinum by fibrous adhesions There was a large deep ulcer in the mucosal

FIG. 4



FIG 5

FIG 4—Photograph taken at autopsy, with the apex of the heart retracted superiorly, demonstrates the greatly thickened pericardium and the 5 x 5 cm gastro-pericardial fistula on the left posterolateral wall of the pericardial sac The gastric mucosal folds are clearly seen through the fistulous opening

FIG 5—Specimen removed at autopsy demonstrating carcinomatous thickening of the wall of the distal esophagus The marginal anastomatic ulcer is well shown and just distal to this the gastric aspect of the fistula appears

surface of the anterior wall of the stomach immediately distal to the site of the anastomosis. This measured 5 cm in diameter and 0.6 cm deep, and its edges were firm. Microscopically the base and edges of this ulcer showed tumor tissue. The large defect described above which opened into the pericardial sac was directly below this ulcer and was separated from it by a band of apparently normal mucosa 1 cm in width.

In addition to the above finding there were small plaques of metastatic adenocarcinoma beneath the serosa of the right diaphragm, gallbladder, ileum, colon and cul de sac.

Anatomical diagnosis Recurrent partially differentiated adenocarcinoma of esophago-gastric junction with metastases to left lung, left pleura, mesentery, peritoneum, and mesenteric lymph nodes, gastro-esophageal anastomosis with marginal ulceration and gastro-pericardial fistula, acute fibrinous and chronic pericarditis, cardiac hypertrophy and dilatation, compression atelectasis of lungs, arterial and arteriolar nephrosclerosis.

Discussion Gastro-pericardial fistula is rare. Gottesman and Benedick² in 1926 reported a gastro-pericardial fistula due to carcinoma of the cardia treated by radium implants, with subsequent necrosis and fistula formation. Abbot¹ in 1945 reported two cases of pericardial esophageal fistula, one congenital and the other occurring between the pericardium and a large epiphrenic esophageal diverticulum approximately six months following transthoracic diverticulogastrostomy. Other pericardial enteric communications have been reported: perforation of the esophagus into the pericardium by a foreign body and perforation of the esophagus into the pericardium by a tuberculous abscess.³

It is probable that the sequence of events leading to fistula formation in this case was postoperative adhesions between the stomach and the pericardial sac followed by invasion of the walls of both organs by residual carcinoma. This carcinoma tissue subsequently became necrotic and sloughed, leaving a direct gastro-pericardial communication.

Indirect evidence that the fistula was due to carcinoma in the stomach and not a pericardial metastasis is that Scott and Garvin⁵ in a series of 11,100 autopsies found metastases to the heart and pericardium in only three cases of 262 tumors of the esophagus and stomach.

The striking "splash murmur" and the characteristic roentgenographic appearance make the diagnosis of hydropneumopericardium relatively easy. The differential diagnosis of air and fluid in the pericardial sac must include bronchopulmonary-pericardial fistula and suppurative pericarditis associated with gas-producing organisms. In this case pericardial aspiration of swallowed methylene blue definitely established the enteric origin of the fistula.

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DIAPHRAGMATIC HERNIA WITH COMPLETE EVISCERATION OF THE LIVER*

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Diaphragmatic hernia has been quite thoroughly discussed in the surgical literature. Congenital herniations are usually diagnosed in childhood, whereas the acquired and traumatic types are most frequently seen in the adult. The case herein reported is unusual in that it represents a pleuroperitoneal hiatus in the right diaphragm of an adult with complete evisceration of the liver and gallbladder. It is of further surgical interest in that it was not diagnosed until serious symptoms developed following a right pyelolithotomy.

The development of the diaphragm is a complex embryologic process, a discussion of which is not pertinent to this paper¹. It is sufficient to recall that the complex developmental evolution makes for many different types of hernia. Classification of diaphragmatic hernia on an embryologic basis is not always possible. Clinically the most simple and useful classification is that of Hedblom⁵. He divides all diaphragmatic herniae into three major groups: Congenital, acquired and traumatic. Further classification into sub-groups is possible but the three basic types satisfy most statistical requirements. Diaphragmatic defects when associated with evisceration of portions of the gastro-intestinal tract produce serious physiologic disturbances. It is significant that our case was asymptomatic until herniation of the colon was added to the evisceration of the liver. Congenital defects of the right diaphragm are much more rarely diagnosed than similar defects on the left. A search of the literature fails to reveal a single case described as total evisceration of the liver. Several cases of partial herniations of the liver through diaphragmatic defects are recorded but they are usually described as being lobular rather than total²⁻⁷. The case described below stimulates speculation as to whether it is possible for the liver to develop above rather than below the diaphragm.

Case Report (R A) A 54-year-old farmer was admitted to the Veterans Hospital, Lincoln, Nebraska, complaining of urgency and frequency of urination, terminal dysuria, dribbling and nocturia. The history revealed that 6½ years previously he had been injured in an automobile accident in which he suffered multiple fractures of the ribs, a fractured left patella and a fractured pelvis. Following the accident he was semi-comatose for two weeks and since that time had a speech defect and residuals of a right hemiplegia. An open reduction of the left patella was carried out and a suprapubic cystostomy was performed. He used an indwelling, suprapubic catheter for approximately

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two years after the accident Following removal of the catheter the suprapubic sinus was closed surgically

Physical examination on admission revealed a small, undernourished, white male who appeared chronically ill He had a speech defect and showed evidence of mental impairment He walked slowly with a shuffling gait The chest was thin, symmetrical, with flaring of the costal margins and considerable muscular atrophy The lungs were resonant and no adventitious sounds could be heard on auscultation The heart was not enlarged to percussion The sounds were normal and of good quality, there were no thrills or murmurs The pulse was 90, regular, and of normal quality and rhythm The blood pressure was 100/70 A right inguinal hernia was present but was not disabling A moderate degree of prostatic hypertrophy was noted The admission blood count was within normal

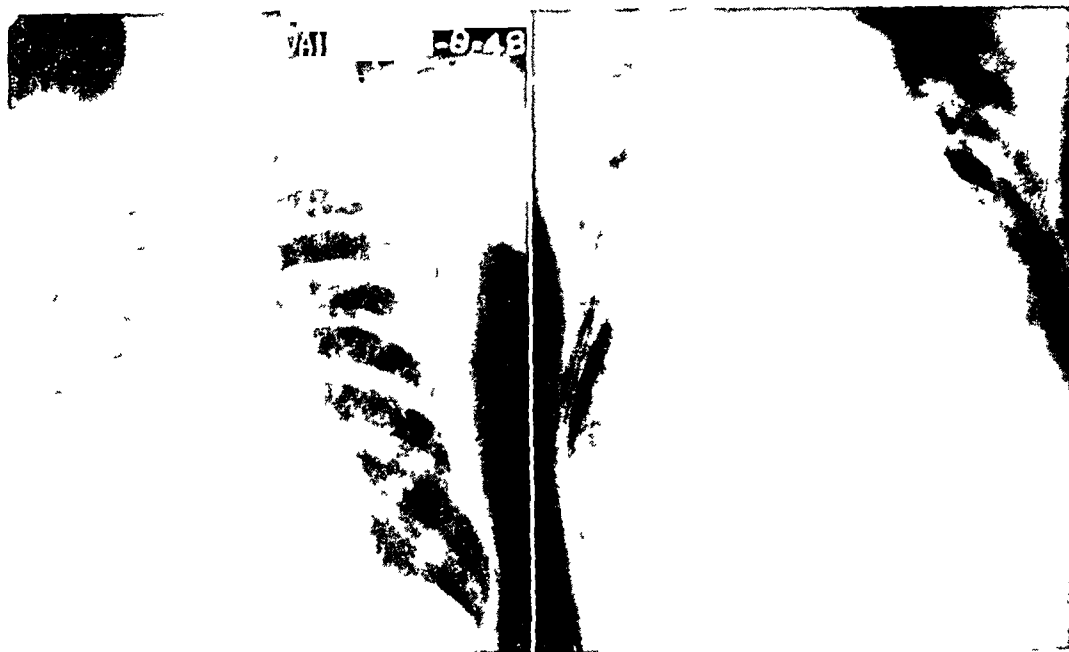


FIG 1

FIG 2

FIG 1—Preoperative roentgenogram Routine chest plate Interpreted as elevated right diaphragm with basal pleuritis

FIG 2—Postoperative pyelolithotomy roentgenogram Chest plate demonstrating large bowel shadow in thorax and absence of liver shadow below costophrenic angle

limits The urine was very cloudy, the reaction was acid, the specific gravity 1.012 and albumin 2 plus Microscopic examination disclosed many white blood cells and culture revealed a mixed flora of colon bacilli and staphylococci Wassermann and Kahn tests were negative

A roentgenogram of the chest showed the trachea to be in the midline with no enlargement or displacement of the cardiac shadow The aorta was somewhat tortuous The right diaphragm was reported to be elevated and a pleural reaction appeared to be present just above it There was an increase in the bronchial markings throughout both lung fields There were healed fractures of the first 6 ribs on the right and what appeared to be a congenital defect in the first rib anteriorly on the left (Fig 1) A roentgenogram of the abdomen revealed a huge amorphous calcium deposit in the region of the right kidney Intravenous urography disclosed bilateral hydronephrosis and hydronephrosis, with a large calculus in the right ureter and renal pelvis

DIAPHRAGMATIC HERNIA

On cystoscopic examination a small bladder with a severely trabeculated wall and a chronic cystitis was found. The ureteral orifices were abnormally located on the posterolateral wall of the bladder and each ejaculated a cloudy urine. The abnormal location of the ureteral orifices was thought to be due to the fact that the bladder was distorted by the previous longstanding suprapubic cystostomy. A diagnosis was made of calculus in the right renal pelvis, renal tuberculosis to be considered.

A right renal exploratory operation (by A. D. M.) revealed an enlarged kidney with an extremely dilated pelvis and ureter containing a huge elliptical calculus. The calculus was removed through an incision in the ureter and pelvis. The stone was yellow-grey in color and friable with a soft, caseous center. Cultures taken from the urine in the pelvis

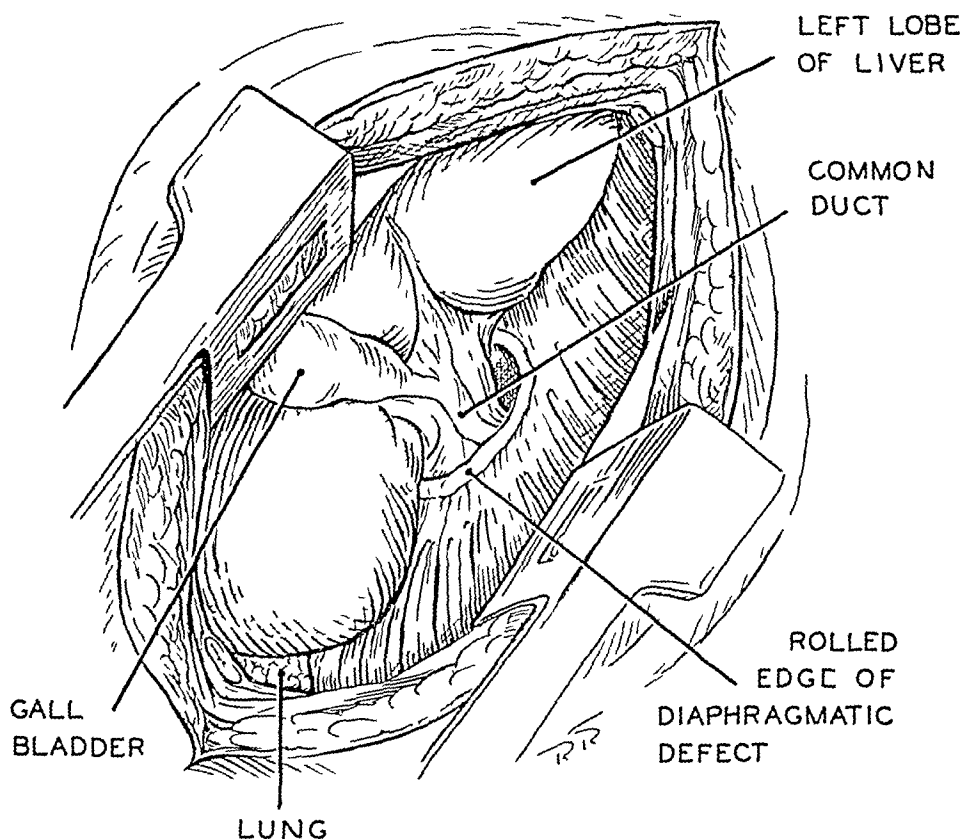


FIG 3—Partially diagrammatic drawing illustrating relationship of liver and gallbladder to the diaphragm. The herniated colon is not shown but entered the chest through the defect anterior to the porta hepatis.

revealed a mixed flora of colon bacilli, staphylococci and streptococci. Smears and guinea pig inoculation showed no evidence of tubercle bacilli. Renal function was good following the operation.

In the evening of the second postoperative day the patient developed a cough and became slightly dyspneic. In the morning of the third day abdominal distention, due to a combination of postoperative urinary retention and ileus, appeared. Despite antibiotics, prostigmine, nasogastric suction and retention urethral catheter his dyspnea and cyanosis increased. Physical examination of the chest at this time revealed a hyperresonance of the right hemithorax. Liver dullness was completely obliterated. There were no breath sounds audible in the right chest except immediately lateral to the sternum. The left lung field was filled with many coarse, moist, breath sounds. A diagnosis of postoperative atelectasis on the right was made. The patient was placed in an oxygen tent, encouraged to cough, and intermittent carbon-dioxide inhalations were prescribed. Roentgenograms

of the chest and abdomen discovered a large, gas-filled colon, extending into the right thoracic cavity producing an atelectasis of the right lung (Fig 2)

Surgical consultation was requested and a diagnosis of right diaphragmatic hernia was made. Because of the respiratory involvement a thoracotomy was recommended. Therefore, in the evening of the third postoperative day the patient was subjected to a thoracotomy under intratracheal anesthesia (by W P K). At operation the entire liver, the major portion of the transverse colon and the hepatic flexure of the colon were discovered in the right pleural space. There was a central defect in the diaphragm through which the organs had entered the pleural cavity. The defect was approximately 10 cm in diameter, perfectly circular and with a thick, rolled edge. The liver was rotated upward

and back and was attached at its apex to the posterior margin of the defect in the diaphragm by means of the central tendon. The gallbladder was present, lying above the liver (Fig 3). It was impossible to return the liver into the abdomen through the existing defect in the diaphragm since the opening was much too small. An incision was made, therefore, extending the defect antero-laterally. The transverse colon was then reduced with ease. The liver was replaced by first inserting the left lobe through the defect in the diaphragm and then gradually manipulating the right lobe of the liver beneath it. Considerable difficulty attended this procedure due to the distended colon which quite completely filled the peritoneal cavity. The defect was closed under considerable tension with interrupted, heavy, nylon sutures. Good and adequate inflation of the lung was obtained and the thoracotomy wound was closed in a routine fashion without drainage.

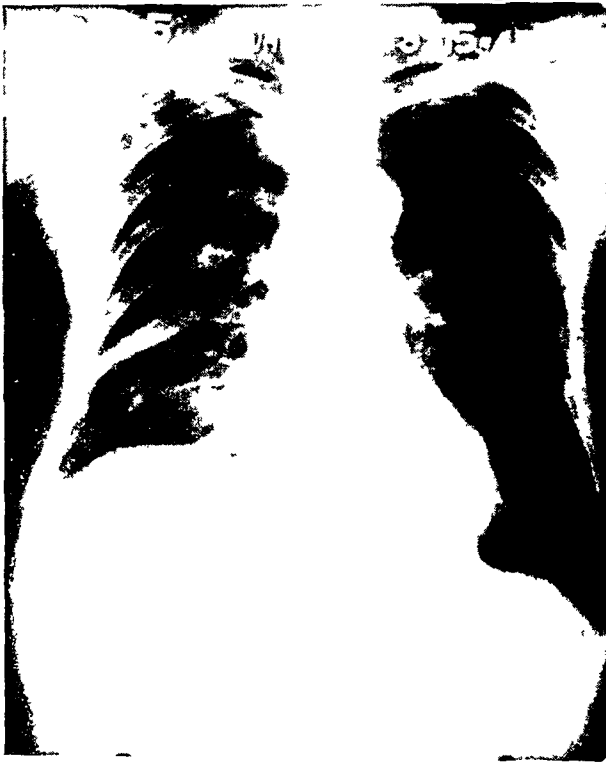


FIG 4—Postoperative thoracotomy roentgenogram. The diaphragm is now seen to approximate its normal position. The liver shadow is now normally situated. The old, healed, rib fractures stand out clearly.

measures to combat this were immediately started. A Miller-Abbott tube was passed, prostigmine and pitressin were given and 8 cc of 20 per cent hypertonic saline solution were given intravenously. Intravenous infusions and antibiotics were continued.

In the first day after the thoracotomy the abdominal distention had been largely relieved and breath sounds could be heard in both lung fields. After the abdominal distention subsided the Miller-Abbott tube was removed. The oxygen tent was discontinued on the fourth postoperative day at which time the respirations were normal and the color was good. He was ambulant on the fifth postoperative day and sutures were removed on the ninth. He improved rapidly but his hospital stay was prolonged because of a persistent urinary infection which was treated with appropriate antibiotics. A postoperative roentgenogram of the chest taken before discharge from the hospital revealed many healed fractures on the right and a resection of the right tenth rib. The diaphragm was elevated and there was some increase in the bronchial markings in the right base (Fig 4).

He was discharged ambulant on the twenty-sixth day after thoracotomy. At that time he was asymptomatic and felt well. He was readmitted and observed five months after his discharge. During the latter admission the urine was found to be infected and he was treated with streptomycin and sulfathiazole. Fluoroscopy of the chest at this time revealed an active right diaphragm with some fixation laterally but no evidence of herniation. He was discharged after treatment for the urosepsis.

DISCUSSION

A study of this case develops several interesting questions as well as emphasizing certain findings. In the first place, it emphasizes the importance of studying roentgenograms not only in order to interpret obvious pathologic conditions but also to evaluate all unusual findings. After a review of the roentgenograms one must conclude that failure to note the absence of the liver shadow in the preoperative scout films was an embarrassing oversight. An important clinical observation is made in that the presence of a defect in the diaphragm with the liver above it is a completely asymptomatic condition. Symptoms relative to the diaphragmatic defect were not produced until postoperative ileus forced distended bowel into the thorax. This suggests that symptoms of diaphragmatic hernia are, in general, associated with disorders in function of the gastro-intestinal tract. Respiratory symptoms are secondary.

The importance of bedside roentgenography in the diagnosis of postoperative pulmonary complications should be stressed. Although an astute diagnostician can quite readily make a differential diagnosis of postoperative pulmonary complications from physical findings alone it imposes a serious burden on the junior staff members who so often see such conditions first. The help that a bedside chest plate offers should not be neglected in the evaluation of serious postoperative pulmonary complications. Without a postoperative chest film the case under discussion might well have been considered a case of massive pulmonary atelectasis.

It is interesting to speculate as to the etiology of the hernia in this case. Certain aspects strongly suggest a congenital origin of the diaphragmatic defect. However, the possibility of a traumatic origin cannot be excluded. Central defects of the diaphragm are rare whether congenital or traumatic in origin. A central defect on a traumatic basis is possibly somewhat more difficult to postulate. It would assume spontaneous healing of a torn diaphragm with the exception of a small opening for the porta hepatis. On the other hand, an embryologic explanation also meets with serious objections. A central defect implies failure of development or fusion of the pleuroperitoneal membrane. Studies of the embryologic development of the diaphragm seem to indicate that the liver and adrenal glands play an important role.¹ It scarcely seems possible for an essentially normal diaphragm to develop below the liver. Finally, we cannot ignore the history of trauma. The violence this patient suffered in the automobile accident was serious enough to be just sublethal. The residuals are still present in the form of cerebral damage, healed fractures of ribs and, indirectly, probably even the renal calculus. A traumatic origin of

the hernia must, therefore, receive first consideration despite difficulties in the interpretation of the findings

SUMMARY

1 An unusual case of pleuroperitoneal hiatus of the right diaphragm is described. It is believed to be the first case reported of a supra-diaphragmatic liver in an adult.

2 The importance of a careful study of all roentgenograms is re-emphasized. If, as in this case, attention is directed exclusively at obvious pathologic lesions, associated conditions will often be overlooked. The judicious use of bedside roentgenography in the postoperative period is also stressed.

3 The etiology of the condition is discussed, although no satisfactory conclusions are drawn. The factors involved in considering this either as a congenital or traumatic form of diaphragmatic hernia are presented. The explanation in either case results in an incomplete description of the course of events.

4 The development of symptoms in the postoperative period due to a patent pleuroperitoneal hiatus is described. The operative treatment and successful outcome of the case are reviewed.

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HOURGLASS STOMACH CAUSED BY ANNULAR MUSCULAR HYPERTROPHY*

REPORT OF A CASE

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Hypertrophy of the pyloric muscle of the stomach is well known in infants, and a number of cases in adults have been reported. However, hypertrophy of the muscular layers of the stomach of the proximal portion of the antrum causing an annular constriction partially dividing the stomach into two compartments, and giving rise to an hourglass appearance on roentgenographic examination apparently has not been reported. The following is the story of such a case.

CASE REPORT

A 74-year-old white male was admitted to the hospital January 17, 1948, with the chief complaint of pain in the epigastrium of a month's duration. This pain occurred an hour or two after meals and was associated with the sensation that the stomach was overfilled and could not empty. There was some nausea with the pain, but no vomiting. The patient lost six pounds during this period. No jaundice, hematemesis, or diarrhea had been noted.

Six years previously there had been similar symptoms which subsided when the patient followed a bland diet.

Previous records showed that the Wassermann test had been positive in 1928. He had received anti-syphilitic therapy. Records since 1945 showed repeatedly negative serologic tests.

Significant points in the physical examination included some mental confusion, a shuffling gait, partial deafness, blood pressure 180/94, palpable liver edge, and some observers noted a non-tender mass in the epigastrium.

The following laboratory examinations were within normal limits: blood count, urinalysis, sedimentation rate, blood and spinal fluid Wassermann, colloidal gold curve of spinal fluid, and serum proteins. NPN was 48. Gastric analysis showed 60° of free acid and 76° total.

Roentgen-ray examination (Dr. T. Pfeffer) of the stomach after ingestion of barium showed a localized deformity in the nature of an annular constriction approximately 2.5 cm in extent near the proximal portion of the pylorus. A freely movable translucent mass 2.5 by 3 cm was present in the stomach proximal to the deformity (Figs. 1 and 2). This deformity was constantly present on repeated examinations.

In spite of the gastric acidity and normal sedimentation rate, a tentative diagnosis was made of carcinoma of the stomach. The movable mass seen in the stomach was thought to be a foreign body, probably, a trichobezoar, or possibly a pedunculated, polypoid tumor.

On February 10, 1948, the patient was operated upon. There were some old adhesions between the omentum, gallbladder, liver and duodenum, and a firm constriction of the stomach approximately 5 cm proximal to the pyloric sphincter. This was about 3 cm

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FIG 2.—Roentgenogram of stomach after partial emptying showing the constantly present defect

FIG 1.—Roentgenogram of stomach showing the hourglass appearance and the area of translucency proximal to the deformity

thick. The overlying serosa was normal. Posteriorly, this area was somewhat adherent to the peritoneum over the pancreas. There were no nodules found in the liver, adjacent ligaments or omentum, and the regional lymph nodes did not seem to be involved in tumor. There was no free fluid.

Because of the patient's age, and because there was some question as to the diagnosis, a partial rather than a total gastrectomy was decided upon. The distal two-thirds of the stomach was removed down to the pyloric ring. The duodenal stump was closed and an ante-colic, anti-peristaltic anastomosis was made between the cut end of the stomach and the side of the jejunum about 30 cm from the ligament of Treitz.

Recovery was uneventful and the patient was discharged March 2, 1948. Since then he has remained free of pain, complaining occasionally of a poor appetite.

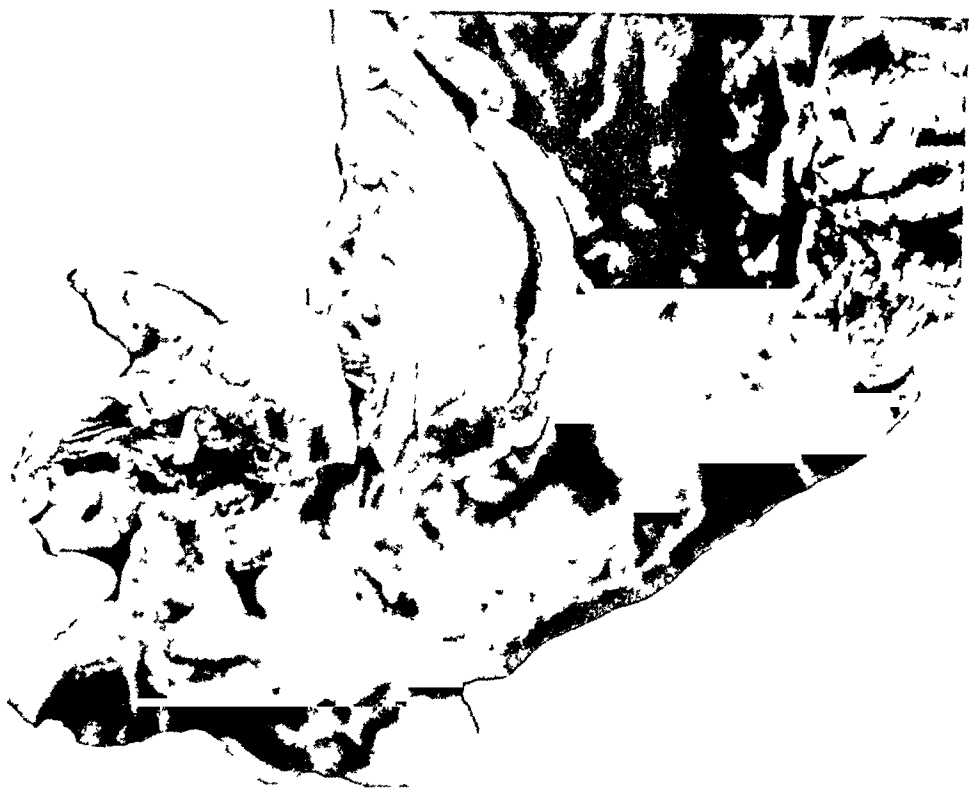


FIG 3—Gross specimen of stomach showing cross-section of thickened muscle

Pathologic Report (Dr Joseph Lubitz) "Gross Upon examination of the specimen, the tumor was seen to be a firm constricting area of thickened stomach wall measuring 2 cm in width, located 4 cm from the pyloric end of the stomach. This thickened band cut with increased resistance, and it was uniformly shiny yellow-white in color. On cross-section of the stomach wall this mass was found to involve the muscularis and measured 7 mm in thickness. At the point of constriction the lumen measured but 1 cm. Between the pyloric end of the specimen and the muscular band the stomach wall was of normal thickness in diameter. A peach pit lay in the proximal portion of the specimen. The mucosa appeared normal throughout (Fig 3).

"*Microscopic* The mucosa is intact. Under the mucosa there is hypertrophy with replacement by fibrous tissue of the submucosa. The thickening of the stomach wall is primarily due to hypertrophy of the musculature. With special connective tissue stains, it can be seen that the fibrous stroma accompanying the hypertrophied muscle is minimal. The serosal surface is only slightly thickened (Fig 4).

"*Diagnosis* Annular constriction due to muscular hypertrophy."

The peach pit accounted for the area of decreased density seen on the roentgen-ray film.

DISCUSSION

Since Beardsley's report of a case³ of congenital hypertrophic stenosis of the pylorus, the condition has come to be a well-known lesion in infants. More recently the existence of a similar lesion in the adult has been recognized



FIG 4—Low power photomicrograph showing thickened muscular layer of stomach wall

and numerous cases have been reported, including a series of 81 cases seen in a four-year period by Kirklin and Harris.⁷ Localized, annular, constricting hypertrophy of the stomach muscle elsewhere in the stomach does not seem to have been reported.

ally the muscular layers of the pyloric antrum are slightly thicker than the remainder of the stomach. The circular fibers are greatly increased in the pyloric sphincter just proximal to the duodenum. In hypertrophy of the pylorus in adults the enlarged muscular mass consists of circular (and oblique) muscle in the antral musculature, separate from and proximal to the normal, pyloric sphincter^{1, 5, 10}. The niche separating the sphincter from the antral muscle is one of the radiologic criteria for diagnosis of pyloric hypertrophy. Ordinarily this hypertrophy extends several centimeters proximal to the antrum, forming a funnel-shaped canal which is widest at its proximal extremity.

Pyloric stenosis in the adult has been attributed to persistence of a congenital pyloric hypertrophy and also to the development later in life of hypertrophy of the pyloric muscle, the cause of which is not clear, but possibly a gastric ulcer which has healed^{4, 11, 12}. The appearance under roentgen-ray has been described and the radiologic criteria for diagnosis have been defined^{1, 2, 7, 9, 10}.

In the above described lesions, however, the point of greatest constriction of the stomach has been in the distal portion of the pylorus. In the case described here the constriction occurred in the more proximal portion of the antrum, causing an hourglass constriction of the stomach into two portions.

The hourglass deformity of the stomach is usually secondary to an intrinsic process, usually benign, but sometimes secondary to neoplasm or to ulcer^{6, 8}. In the present case the mucosa was intact. There was no scar tissue. Further evidence of ulcer was lacking. The lesion was entirely in the muscular layer. Interpretation of the roentgen-ray films led to a diagnosis of carcinoma of the stomach. The hypertrophy of the muscle remains undetermined.

It is probable that the short duration of symptoms was due to the ingestion of a peach pit and the resultant intermittent obstruction of the pyloric area.

SUMMARY

There is described of annular constriction of the stomach caused by hypertrophy of the musculature proximal to the pyloric region giving rise to an hourglass stomach which resembled carcinoma upon roentgen-ray examination.

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COARCTATION OF THE AORTA AT THE LEVEL OF THE DIAPHRAGM*

CASE REPORT

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SINCE CRAFOORD'S REPORT in 1945¹ describing a successful surgical procedure for coarctation of the aorta, there has been increased interest in this congenital vascular anomaly Gross,² Crafoord³ and others^{4, 5} have reported successful operations in an appreciable number of cases

The infantile type of coarctation of the aorta is usually not compatible with life Those patients who survive infancy and childhood have the adult form of coarctation, which is manifest by a stenotic segment, most often located between the left subclavian artery and the ductus arteriosus or ligamentum arteriosum Variations in location occur a few millimeters in either direction

This case report is that of a young woman who at operation was found to have a coarctation of the aorta just above the diaphragm (Fig 1) Investigation of the literature revealed that Schlekat⁶ in 1933 reported such a case in a 44-year-old man His patient died with a diagnosis of aortic insufficiency Autopsy revealed a coarctation of the aorta just above the diaphragm The stenotic segment was narrow and its lumen admitted only a 3 mm probe The aorta above the stenosis was enlarged and below was of about normal size The collateral arterial channels were dilated Costa⁷ in 1930 described a stenosis of the aorta between the first and second intercostal arteries Hickl⁸ in 1931 reported a constriction of the aorta located below the ductus arteriosus measuring 6 cm in length This was considered as probably inflammatory in origin Our case is, apparently, the second one, in the low thoracic aorta, to be reported, and the first one for which an operation was performed

CASE REPORT

The patient, 20 years old, was admitted to the John Gaston Hospital on February 18, 1948 Since July, 1947, she had been troubled with attacks of dyspnea, palpitation, and tachycardia Exercise or excitement increased these symptoms, the attacks lasting only a few minutes She had had severe headaches since the age of nine years Episodes of pain in her arms and legs had occurred since November, 1947 She was handicapped to the extent that she could not do much housework The past history was non-contributory

Physical examination revealed a well developed young colored female The arterial pulsations in her neck were increased bilaterally The blood pressure in her left arm was consistently higher than that of the right arm, and varied between 180/140 and 200/140 The pressure in her right arm varied between 120/100 and 130/100 Blood pressure readings were never obtainable in her legs nor were pulsations ever palpable Her heart was questionably enlarged and a systolic murmur was heard posteriorly over

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the tip of the scapula. There were no palpable pulsations of the intercostal arteries. Her RBC was 4,600,000, hemoglobin $12\frac{1}{2}$ Gm, blood Kahn negative. Roentgenogram of her chest revealed a moderate enlargement of the heart, the contour indicating left ventricular enlargement. Minimal erosions were reported on the inferior surfaces of the fourth, fifth, sixth, and seventh ribs bilaterally. The aortic knob was present but not prominent. The lung fields were clear. A preoperative angiocardigram was attempted, but was unsatis-



FIG 1.—Drawing to demonstrate the low position of the coarctation

factory. The clinical diagnosis was coarctation of the aorta, and on March 10, 1948, operation was performed.

Operation. Under cyclopropane endotracheal anesthesia, an approach was made through the left chest by dividing the intercostal muscles in the fourth interspace. Posterior segments of the third, fourth, fifth, and sixth ribs were removed. On freeing the parietal pleura, a dilated aorta was found, with no constriction. Pulsations of the aorta were quite forceful. The left subclavian artery was not enlarged. As far as the thoracic aorta could be visualized, no constriction was present. The intercostal arteries were not

dilated. The low thoracic aorta could not be visualized, but by palpating low in the chest, there was thought to be a constriction in the aorta just above the diaphragm. An actual constriction could not be felt, but the pressure in the low aorta at the level of the diaphragm seemed to be definitely less than that of the aorta above, and a point of merging from one pressure to the other could be localized to an area of about one finger's breadth in the aorta. Three diodrast angiograms were made on the operating table by injecting directly into the aorta, but the portable roentgen ray, due to its low power, failed to reveal any filling of the aorta. In view of the low level of the coarctation it was considered advisable to terminate the operation and approach the area later through a more suitable incision.



FIG 2—Cross-section of specimen showing marked thickening which is chiefly intimal. Separation of the intima and media can be seen.

Second Operation. On April 9, 1948, operation was performed at a lower level in the left chest. A postero-lateral incision was made parallel to the ninth rib with resection of posterior segments of the seventh, eighth, and ninth ribs. Exposure was difficult because at this level the aorta was lying directly over the vertebral column in the midline. A coarctation was found, approximately 5 cm above the diaphragm. The diameter of the aorta above the site of coarctation was the same as that below, the aorta in this region, however, was somewhat smaller than the aorta higher in the chest. Very little blood was passing through the stenotic area, judging by the absence of pulsations in the aorta below. The intercostal arteries, above and below the stenotic area, were of normal size. There was concern over probable difficulty in approximating the aortic ends since the stenotic area was rather long and the aorta rigid. The Bradshaw clamp⁹ was applied and the stenotic segment measuring 17 mm in length was excised. The lumen of the specimen

at the maximum point of constriction was 4 mm in diameter (Fig 2) The ends of the aorta were under considerable tension and could not be approximated The proximal Bradshaw clamp began slipping and it was necessary to apply the modified Moynihan clamp, recommended by Gross, to the proximal aorta This clamp held very well but still the aortic ends could not be brought together The aorta had no elasticity at all Four or five sets of intercostal arteries were divided until 12 cm of aorta was mobilized This did not permit any further motion of the aortic ends Since it was impossible to join the ends of the aorta an iliac vein graft¹⁰ was considered as a bridge for the defect, but the patient had been under anesthesia for five hours and was developing pulmonary edema The extra time which would be necessary for procuring such a graft was considered out of the question, and there was no assurance that such a graft would withstand the increased pressure of the aorta without rupture or subsequent aneurysm formation No plastic prosthesis¹¹ was available Under the circumstances, the only choice left was to close the ends of the aorta with sutures, hoping that the collateral circulation would be adequate The patient died approximately five hours after the operation Permission for autopsy was refused

DISCUSSION

The etiology of coarctation in the low thoracic aorta can not be explained on the basis of existing theories¹² of which we have any knowledge The most widely accepted theory of Skodiak,¹³ dealing with the extension of an obliterative process from the ductus arteriosus into the aorta, would not be applicable in this case The possibility of inflammatory origin of the stricture is not borne out by microscopic study of the specimen

The unusual location of the coarctation in this patient was not suspected until failure to find a constriction in the upper thoracic aorta, at the time of the first operation, led to further exploration The radiographic report of the presence of an aortic knob had been commented upon prior to operation, yet the arch was not prominent, and in a fair percentage of cases of high coarctation the arch can be seen on roentgen ray examination It is doubtful, therefore, that visualization of the aortic arch should necessarily lead one to suspect a low coarctation

Three attempted diodrast angiograms during the operation failed to outline the low aorta This failure was due to the low power of the portable roentgen ray used It might be pointed out that relatively small, 21-gauge, needles were inserted obliquely into the aorta for the injections, and following withdrawal of the needle each time, blood spurted from the aorta for a distance of six to ten inches, and could be controlled only by the use of gelfoam sponges, and even then with difficulty In view of this experience I would question the safety of a blind insertion of an 18-gauge needle into the aorta, through the back, as recommended by some,¹⁴ for the purpose of obtaining an angiogram in patients with increased aortic pressure

There was consistently a distinct difference in the blood pressure of the two upper extremities, with the greater pressure in the left arm The blood pressure in the left arm varied between 180/140 and 200/140, while that in the right arm was 120/100 to 130/100 Reifstein¹⁵ noted that, uncommonly, there might be a marked difference of circulation of the two upper extremities

This usually consists of a decreased circulation in the left arm because of encroachment upon the orifice of the left subclavian artery by the coarctation, which results in partial occlusion of that vessel. King¹⁶ in 1939 reviewed blood pressure readings in 170 reported cases of coarctation and added five more cases to the literature. There were only ten cases in which a significant disparity of pressure in the two arms was present, and of these ten patients nine had higher pressure in the right arm, possibly due to involvement of the isthmus of the aorta and the mouth of the left subclavian artery in the same fibrotic anomaly—an explanation offered by Parkes, Weber and Knop.¹⁷ East¹⁸ reported one case in which the blood pressure in the left arm was 195/145 and in the right arm was 135/100. No autopsy examination of the patient was made, however. In a second case, upon which clinical observations were not available, autopsy revealed stenosis of the isthmus of the aorta and an anomalous origin of the right subclavian artery which might have resulted in interference to the circulation of the right arm. Love and Holmes¹⁹ in 1939 reported a case with a blood pressure in the left arm of 210/95 and in the right arm 150/90. At autopsy the right subclavian artery, at its origin from the innominate, was stenosed.

In our case the right chest was not explored and permission for autopsy was refused, so there was no opportunity to examine the right subclavian artery.

Another unusual feature of this case was the absence of dilatation of the intercostal arteries in the left chest. Since approaches were made in both the upper and lower chest on the left, a satisfactory view of most of the intercostal arteries was possible. The roentgen ray diagnosis of rib notching was obviously in error. Possibly, the internal mammary artery served as the major channel for collateral blood.

A distressing finding at operation was the lack of elasticity of the low thoracic aorta. This feature was noted before the coarctate segment was excised so that a minimum length of the strictured vessel was removed, the resected segment measuring 17 mm. in length. In both cut surfaces the intima and media separated and the aorta was pipelike in consistency. The aortic ends could not be approximated and extensive division of intercostal arteries did not give additional mobility. In the upper aorta, freeing of the arch and the left subclavian artery usually permits some straightening of the aortic arch with the result that additional length can be obtained for the proximal aortic segment. No such movement was possible in the low thoracic aorta of this patient.

Substitution of some material is obviously necessary in instances where a rigid aorta is present and the aortic ends cannot be approximated. The use of a vein graft as recommended by Blakemore was considered in this case but was not used for reasons mentioned earlier. Plastic prostheses have been used by Hufnagel in dog's aortas, but its value in human beings for permanent intubation is open to question. In past years many metals and plastics²⁰⁻²²

have been used as substitutes for defects in large arteries, with generally unsatisfactory results Gross^{23 25} recently, both experimentally and clinically, has used preserved arterial grafts with success This method appears promising and would have been the technic of choice in the case reported here if such a graft had been available

SUMMARY

A case is reported of coarctation of the low thoracic aorta just above the diaphragm Apparently, this is the first such case for which surgery was attempted, and the second case in which coarctation has been found in that position

The unusual features of the case and its surgical problems are discussed

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(Continued on page 1118)

UNILATERAL MACROSTOMIA*

A CASE REPORT

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THIS CASE of macrostomia is reported because of its rarity, only five cases having been reported in Europe since 1881. No cases have been reported in America. The condition is generally held to be a fusion fault of the mandibular and maxillary processes, producing a cleft cheek in the same general manner as the fusion fault of the maxillary and naso-frontal processes produce a cleft lip. All the cases reported, including the present one, have been unilateral.



FIG 1—Preoperative view showing deformity

In 1881, Dr J H Morgan¹ presented two cases of macrostomia that had been seen and operated upon. Both of these were closed in a straight line. The next case is reported by Clarke in 1900.² This case had an associated deformity of the hand. In discussion of this case, the group assumed that the child had its hand in its mouth in utero. In 1910, Sidoun³ reports a case from Paris in which there was accompanying deformity of the ear on the same side. In 1936 Eitner⁴ reports a case also complicated by gigantism of the ear with supernumary pre-auricular buds. In this latter case the mouth on

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the normal side measured 2.8 cm from the midline and 4.6 cm on the affected side

CASE REPORT

(E R)—The patient was a 16-month-old female infant, the third child of healthy parents. The other children had no deformities and the parents could recall no other members of the family that had any deformities. The patient was a full term normal delivery. The deformity was noticed at birth and the mother stated that it seemed larger then, in relation to the size of the head, than at time of this examination.

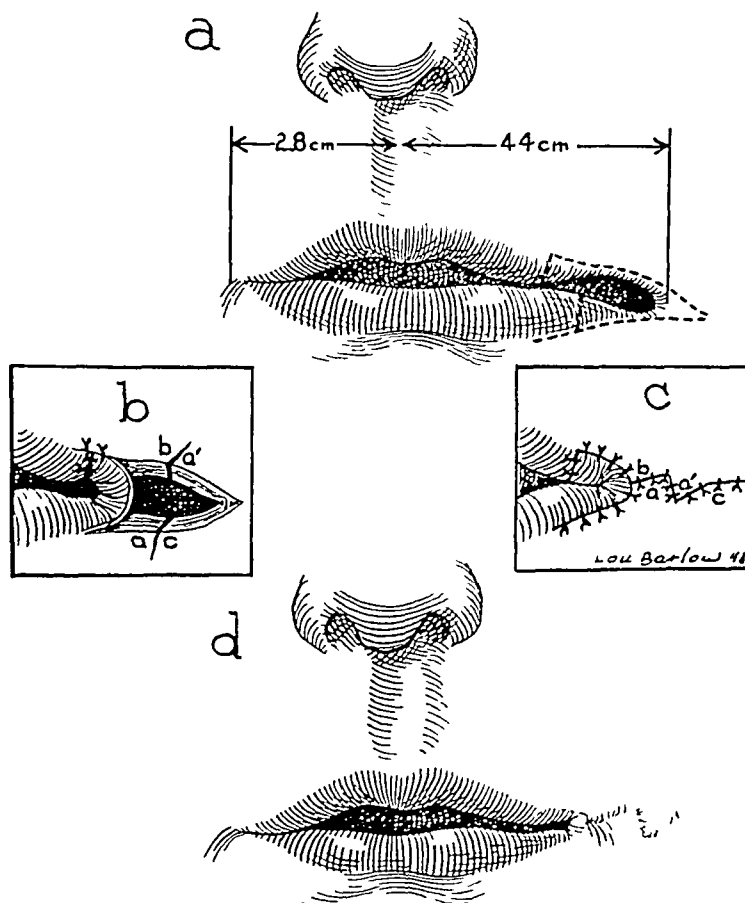


FIG 2—Operative Procedure
(a) Proposed incisions
(b) Vermilion flap rotated for commissure. Incisions for z-plasty
(c) Closure of z-plasty
(d) Result

Physical examination revealed a well-nourished and, except for the mouth deformity, a well-developed child. There were no other deformities. The macrostomia was on the left side, the abnormal commissure being 1.6 cm farther on the cheek than the normal commissure. The exact measurements from midline to commissure on the right were 2.8 cm and on the left, 4.4 cm.

The patient was operated upon under general anesthesia using ether via nasal endo-tracheal intubation. Measurements equal to the normal side were marked on the vermilion border of the affected side. A small section of the vermilion of the upper lip medial to the marking of the new commissure was excised. A small flap of vermilion from the lower lip lateral to the marking was elevated and swung up and around into the

defect on the upper lip forming a new flexible commissure. The remainder of the vermillion of the macrostomia was excised. The orbicularis oris was identified and mobilized. The upper and lower portion were sewn together behind the commissure. Angular incisions were then made in the edges of the remaining cheek defect, producing two small pointed flaps which were transposed and a z-plasty was done. This was to avoid a linear scar pull on the corner of the mouth.



FIG 3—Postoperative view showing symmetric mouth

The final result is good. The mouth is symmetric and water tight. Movement and expression is normal. The skin scars leave something to be desired and may have to be revised later.

SUMMARY

A case of macrostomia, a rare congenital defect, is presented together with the method of surgical treatment.

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BASAL CELL CARCINOMA OF THE ANUS*

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WE HAVE been able to find only eight reported cases of basal cell epithelioma of the anus (see Table I) Rosser,¹ in a review of the literature since 1915, referred to a basal cell carcinoma arising in a fistula In 1933 Buie and Brust² reported 2939 malignant lesions of the anus and rectum encountered during a 13 year period at the Mayo Clinic, 51 of this group were primary

TABLE I

Author	Age	Sex	Clinical Findings	Treatment	Outcome
Tucker and Hellwig 1938	43	M	Early, less than 2 cm Origin in hair follicle	*Local excision radium	No recurrence at 3 years postop
Guess 1935	52	M	Early, 2 cm	*Local excision radon seeds	Died of coronary occlusion at 5 years postop, no sign recurrence
Gabriel 1946	70	M	Early, 1-2 cm Diagnosed by biopsy prior to surgery	Excised by cutting diathermy	No recurrence one year later
Buie and Brust 1933	53	F	Advanced size of orange, also extensive mass in left groin	Radium advised, went home without treatment	Unknown
Buie and Brust 1933	53	F	Advanced, annular lesion	Colostomy and posterior resection, half vagina and local nodes removed	Recurrence 8 mo Death 9 mo
Lawrence 1941	73	M	Advanced, hard annular fungating neoplasm (at operation found to invade prostate and membranous urethra)	Loop colostomy and posterior resection of anus and rectum	Died in 2 years
Lawrence 1941	73	M	Advanced, annular, fungating, completely involving anus and extending at least 2 cm into adjacent perineum and peri-anal tissues	Colostomy and posterior resection of anus and rectum	Died several days postoperatively, no autopsy
Rosser 1931	No mention	No mention		No mention	No mention

* Local excision prior to establishing diagnosis by tissue study

anal neoplasms, and of the 51, only two were basal cell cancers In 1935 Guess³ described one basal cell epithelioma, he made the observation that among 150,000 biopsies at the State Institute for Malignant Disease at Buffalo there were no others reported Tucker and Hellwig⁴ in 1938 reviewed 951 cases in which every specimen at anorectal operation was examined micro-

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scopically, only one basal cell cancer was found in this series. In that same year Gabriel⁵ described his only case, and in 1941 Lawrence⁶ reported two cases.

The early diagnosis of anal basal cell carcinoma presents considerable difficulty. Only one of the three early lesions reported (see Table I) was diagnosed by biopsy preoperatively. A basal cell tumor of the anus does not readily lend itself to biopsy since the growth tends to grow away from rather than toward the surface of the anal mucosa. When this tumor is observed in its early stages it may easily be mistaken for any one of several common benign lesions such as a simple anal ulcer, a fibrosed varicosity, an aberrant lymph



FIG 1—Biopsy basal cell carcinoma beneath mucus glands of the rectal mucosa. The cancer cells are distributed in typical disorderly masses with a single columnar layer of tumor cells at the periphery of the growth. Hematoxylin and phloxine stain. $\times 274$.

node, or even a small, circumscribed, low-grade marginal abscess. Because of the rarity of this tumor, we wish to report another case, with the hope that accumulated experience may lead to improved diagnosis and therapy.

Case Report. K. M., a married, white female, 62 years of age, was seen November 17, 1947. She complained of itching and irritation of the skin around the anus, but only on this date was it severe enough to prompt her to consult her family physician. On routine digital examination this physician noted a little induration beneath the mucosa in the left anterior quadrant between the external and internal sphincters and referred her to one of us (B. D. L.). In the past she had occasionally noticed a trace of fresh,

red blood with bowel movements, she gave no history of passing any old, dark blood or clots. She had no pain with bowel movements, no protrusion except for skin tags, and no change in bowel habit. She had no previous rectal surgery, no loss of weight, and gave no history of cancer in her immediate family.

Findings (November 17, 1947) On digital examination a small area of thickening about 1 cm in diameter could be felt beneath the mucosa at the two o'clock position, at the pectinate line. A biopsy was taken and reported as follows: "Rectal mucosa at the muco-cutaneous junction. There is active mitotic activity but no cell undifferentiation in the squamous epithelium. The sub-epithelial connective tissue contains large pyknotic nuclei of doubtful significance. Another biopsy is recommended."

On November 29, 1947, the biopsy was repeated and described as follows: "Rectal mucosa showing chronic inflammation." On December 4, 1947, the patient was referred to the Tumor Clinic at the Binghamton City Hospital for consultation. The Tumor Clinic made this observation and recommendation: "On the left anterolateral wall about 1½ inches from the anal orifice, there is an indurated area about the size of a dime, this is non-tender and feels deep to the mucosa. At the center of the involved area is a small ulceration, likely the site of biopsy. Our impression is of chronic inflammatory tissue following thrombosis and subsequent fibrosis of internal hemorrhoids. This area should be re-checked in three months."

On March 9, 1948, the area of thickening and induration had increased in size, now measuring 2 cm by 1 cm. A third biopsy was taken and described as follows: "Basal cell carcinoma. The growth in the section lies beneath rectal mucus membrane."

On March 26, 1948, the growth was locally excised and the wound bed generously fulgurated. Microscopic examination of the tissue removed revealed basal cell carcinoma. The growth could not be traced into continuity with any skin appendage. There were also areas of intraepithelial carcinoma in the surface squamous epithelium near the muco-cutaneous junction. By June, 1948, the wound was healed, she was referred for irradiation and received locally, by cone, a total of 5500 r. When last seen in November, 1948, the affected area showed only a small soft scar. She never had palpable inguinal nodes.

SUMMARY

1 With the case described herein, a total of nine cases of basal cell carcinoma of the anus have been reported.

2 With early diagnosis and local surgical excision of the lesion, with or without subsequent irradiation, the prognosis in basal cell cancer of the anus appears to be excellent. The prognosis in advanced lesions appears to be poor.

3 The diagnosis of basal cell carcinoma of the anus may require repeated biopsies of the suspected lesion.

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A COMPACT CAMERA AND LIGHT SOURCE FOR PHOTOGRAPHY UNDER STERILE CONDITIONS*

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A PRACTICAL METHOD for making photographic records of neurosurgical procedures under sterile conditions was described by Ingraham and Cobb in 1947¹ A 35 mm camera (Kodak Bantam Special) equipped with a portrait lens was attached at operation to an autoclaved metal frame carrying a sterile cloth cover that could be pulled over the unsterile camera and secured with a drawstring Focusing was achieved with a rigidly attached metal rod that indicated both the object distance and the center of the lower border of the photographic field Satisfactory black and white and Kodachrome pictures of a motionless field were obtained with the regular operating room light (Fig 1)

This equipment is very simply constructed and is relatively easy to operate † With reasonable care, excellent photographic records may be secured at very low cost There are, however, certain ready modifications that increase the flexibility of the apparatus

1 Standard operating room lights illuminate the field somewhat unevenly, have a color temperature different than that for which 35 mm type A Kodachrome (or other color films) is designed, and are insufficiently intense to allow the rapid exposures required in thoracic and other surgery where motion is a prominent feature This problem of providing an adequate intensity of color corrected illumination has been resolved in a simple and practical fashion by attaching a mushroom flood bulb (General Electric Photoflood RFL 2) to the camera frame by means of a removable bracket (Fig 2). The light bulb is screwed into a standard commercial rubber covered socket rendered waterproof by a tightly fitting rubber gasket that surrounds the screw end of the bulb The light bulb on its bracket is easily detached from the camera frame proper so that it may be sterilized separately by immersion in Zephiran hydrochloride (1 to 1000) (Fig 3) The camera frame is autoclaved in the usual fashion and the two are reassembled at operation Control of the camera light in the operating room is secured safely by employing a mercury switch operated with the foot ‡ The camera is first placed in the proper position for the

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† Complete metal frames and cloth covers for several types of 35 mm cameras are now available at Alfred Bicknell Associates, 243 Broadway, Cambridge, Massachusetts

‡ A satisfactory mercury type of foot switch is manufactured by C M Sorensen, Inc, 403 East 62nd Street, New York 21, New York

COMPACT CAMERA AND LIGHT SOURCE

pictures, then only is the foot switch depressed and the picture snapped. The light is on for one to five seconds only and the bulb does not become hot in this brief time.

The light produced by this attached flood bulb is much greater than that secured by more conservative means and is very constant in intensity and quality. Despite the fact that the bulb must be offset somewhat from the axis of the camera lens, the many reflecting surfaces present in the freshly draped operative field cause sufficient light scatter to produce surprisingly flat illumination. Excellent 35 mm Kodachrome pictures of the rapidly beating dog

FIG 1

FIG 2

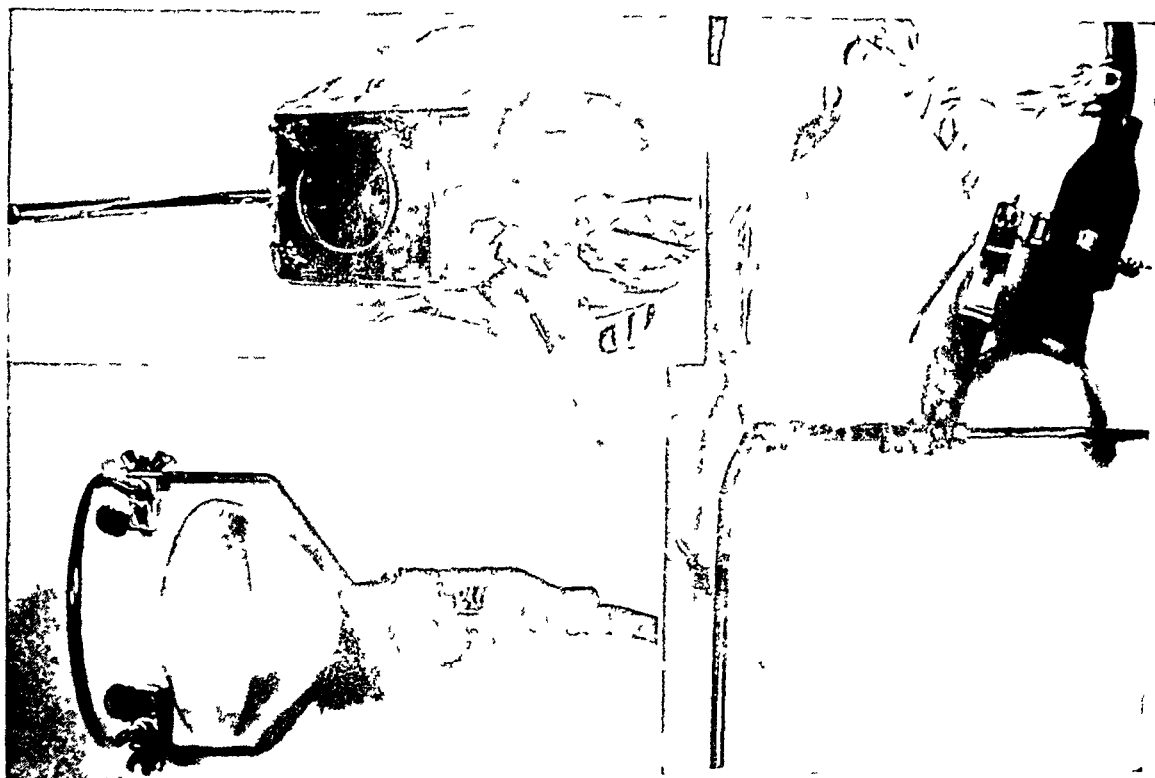


FIG 3

FIG 1—Sterile camera of the Ingraham and Cobb type ready to be used. The cloth bag, metal frame, and glass window completely enclose the camera (Argus C-3). The firmly attached metal rod determines both the object distance and the field size.

FIG 2—The same camera shown in Figure 1 with attached light source.

FIG 3—The bulb, socket, and bracket shown in Figure 2 have been detached from the camera frame. This requires the loosening of but two wing screws.

heart have been repeatedly obtained in the laboratory with the above equipment, and thoracic vascular procedures have been photographed in the hospital using the camera shown in Figure 5.

The proper speed and diaphragm opening must initially be calculated by trial and error for each photographic field size, but once obtained, may be relied upon. It has been possible, for example, using 35 mm type A Koda-

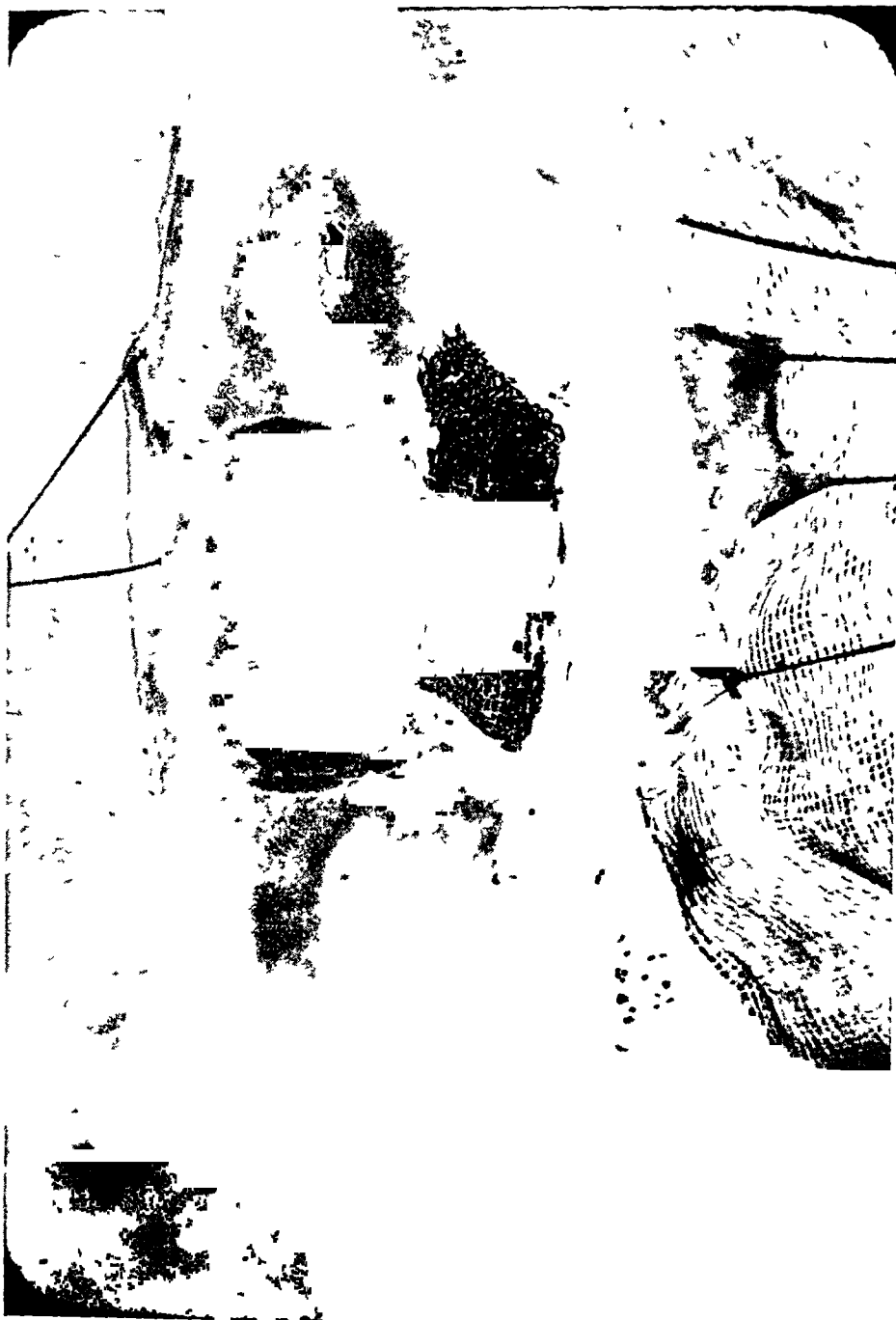


FIG 4.—Black and white print from an original 35mm Kodachrome transparency taken under sterile conditions at operation. The picture represents a completed human blood vessel graft for correction of coarctation of the aorta. Approximately natural size. (Courtesy Dr Robert E Gross)

chrome, a field of four by six inches, and a diaphragm of f-9 to use shutter speeds of 1/60 to 1/100 second (Fig 4) Where great depth is desired, the diaphragm may be closed further at the expense of the speed

2 The field size is limited to approximately six by eight inches when a three diopter "portrait attachment" is used with the 50 mm focal length lens of a 35 mm camera, and this is frequently much larger than is desired By employing a camera with a removable lens such as a Leica, Contax, etc, it is possible to obtain a field of any desired size by simply placing extension tubes of different lengths between the camera and the lens² Proper orientation of the camera with respect to the field to be photographed can be effected by employing replaceable or adjustable metal focusing rods rather than a single

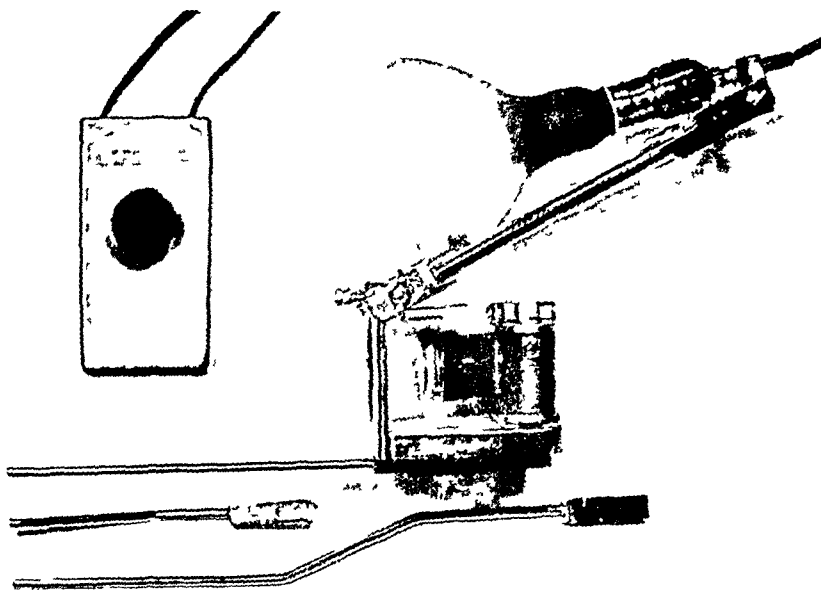


FIG 5—Operating room camera modified from Ingraham and Cobb Note the varying lengths of the focusing rods to conform to different field sizes, the extension tube between camera and lens, and the mercury type of foot switch This particular camera is operated by an unsterile assistant, only the focusing rod itself being autoclaved (Courtesy Dr Robert E. Gross)

fixed one Figure 5 illustrates a camera recently constructed for maximum versatility This employs a Leica III with a lens of 50 mm focal length The field sizes obtainable vary from one and one-half by two and one-quarter inches to six by nine inches, thus providing a more nearly correct field for varying types of operations and for gross specimens of different dimensions A satisfactory "sterile" operating room camera with a lens of 73 mm focal length and a rod adjustable in two planes for different photographic fields has also been used extensively by us The cameras with removable focusing rods may be operated by an unsterile assistant, only the rods themselves being autoclaved

SUMMARY

Two modifications of the "sterile" operating room camera designed by Ingraham and Cobb are described 1 The use of a mushroom photoflood bulb

and bracket sterilizable by immersion in Zephiran and activated by a mercury type of foot switch is discussed 2 A means of decreasing and varying the photographic field size by employing extension tubes in cameras with replaceable lenses is presented These modifications greatly enlarge the range of usefulness of the "sterile camera" as a means of recording operative events

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THE VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland The Award will be made at the annual meeting of the Association which will be held in Houston, Texas, March 9, 10 and 11, 1950, providing essays of sufficient merit are presented in competition

The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length, must be presented in English, and a typewritten double spaced copy in duplicate must be sent to the Corresponding Secretary, Dr George C Shivers, 100 East St Vrain Street, Colorado Springs, Colorado, not later than January 15, 1950 The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend The essay will be published in the annual Proceedings of the Association

Editorial . . .

THE FULL-TIME TEACHER OF SURGERY

A LITTLE MORE THAN 35 YEARS have now elapsed since the General Education Board appropriated funds for carrying out the "full-time scheme" for clinical education and research at Johns Hopkins. It was an action received with great enthusiasm by some and marked hostility by others. Few, indeed, interested in medical education remained neutral. Such was not unexpected, for the fact that the entire staff in the clinical branches should devote full time to teaching and research seemed to many revolutionary in scope, and the medical profession, as a rule, accepts revolutionary changes with what often is a tantalizing hesitation.

Whether the full-time teacher was to be the answer or not, many thoughtful people at that time realized that the clinical departments in our medical schools were in bad need of reform. As a rule, the clinical chief had been the successful local practitioner in his community. When he received his appointment, he retained it until retirement or death intervened. Because he was a successful practitioner, he usually was a busy practitioner, and because of the pressure of time his teaching generally consisted of a series of lectures, clinical demonstrations, or operations. To pursue the scientific side of surgery without adequate time, facilities or budget was indeed difficult. In a period of great scientific achievement, this obviously was an impossible situation. With sciences such as physiology, physiologic chemistry, pathology, and bacteriology making rapid strides, it was patent that soon the surgeon must be cognizant not only with their advances in order to adapt them to his profession but that he also must be a participant in these advances.

Just when the unrest began is hard to state. In Germany in particular, the participation of the surgical teacher in the study of pathology and bacteriology and the withdrawal from a consultative practice was becoming more and more frequently seen. In this country Mall played an important part, bringing back as he did the enthusiasm that was generated by Ludwig and his group in their consideration of clinical medicine as a biologic science. Certainly Mall was a great stimulus, along with Barker, to the group in Chicago, and he carried this fire with him to Johns Hopkins. However, it is perhaps to the vision and tenacity of Welch and the sympathy and sagacity of Gates and Abraham Flexner of the General Education Board that this plan was put in practice in this country as rapidly as it was. During its incubation, however, through the early years of this century, many important medical educators made statements favoring such a form of teaching, some in definite phrases, and others more haltingly.

Although he subsequently came to lose much of his enthusiasm for the full-time plan, the theoretical advantages were expressed by Barker as giving

clinical teachers adequate material on the wards, laboratory facilities, and time for thinking, research, and teaching. On those rare occasions in which the clinical head would find it necessary to take care of a patient with means to pay, the fee would be placed in the treasury of the university. This would throw the accent in the clinical departments on scientific study of the ill person and by so doing would stimulate the undergraduate and graduate student of medicine to further advances in the adaptation of the preclinical sciences to the hospital ward.

This idealism was challenged by the Council of the American Medical Association in its report in 1914. While it granted that the clinical professor should be a great physician, a well-trained teacher, and a research worker, the Council favored the adoption in this country of the system extant in Germany at that time in which the clinical professorship was vested with all of the prerogatives of any other university professorship but the individual occupying the chair was allowed to support himself and his department by private practice. They felt that having the head of the department receive no fees and turning the income from his private consultations in to the university treasury was "grotesque."

Even Welch noted objections to the proposal which he so ably championed. He felt that there would be difficulty in securing and holding the very best men with such salaries as could be paid, and at the same time he felt "it would be hazardous to start the new arrangement with young men in the clinical chairs without considerable experience and without established reputations, however promising they may be." He also was aware of the danger of private practice with a man of such reputation and felt "that the number of these private patients should be limited and determined mainly by the scientific interests of the cases." He also noted that since the attraction of these clinical chairs would be an opportunity for a high type of scientific work and not salary, it was important that the occupants not be "overburdened with administration, teaching, and the care of patients."

Even the most enthusiastic champion of the full-time system felt the inadvisability of excluding the excellent clinical teacher who, to a large extent, was engaged in private practice. He was to give part of his time to teaching, for not only were there many such excellent teachers but this plan would make the budgetary demands not too formidable.

The original plan obviously was an experiment. Since its inception, however, it has been adopted in principle by many institutions in this country, although often there have been modifications. Its effect on medical education undoubtedly has been profound, and the caliber of scientific investigation, teaching, and clinical care emanating from such departments of surgery has been outstanding. A new generation of surgeons has arisen in this country, and the American universities have become the mecca of the surgical world. One, however, should not be too enthusiastic in giving all of the credit to this full-time system, for there are too many brilliant exceptions. Important con-

tributions to the science of surgery have been made by the so-called part-time surgeon as well as in some of our great surgical clinics where there is no undergraduate instruction. There also are many departments of surgery adhering more or less to the old Germanic system that could well be envied by departments manned by full-time professors. The achievements of a great individual should not be credited to a system, for he probably would have done as well under any of the systems, providing adequate facilities were available.

Full-time surgical education undoubtedly has added greatly to the expense of conducting a medical school. During that period of American life in which endowments brought in good returns and in which the wealthy frequently gave large sums of money to medical schools, this rise in cost, to a large part, could be defrayed by increase in income. This source of revenue now is dwindling rapidly. Many schools, therefore, particularly those that are privately endowed, are being confronted with the problem of how to maintain full-time teachers in clinical medicine. So great is this financial burden that once again the question is arising as to whether or not it is desirable that this be done. Complicating the situation even further has been the growth of group practice systems in this country, health and hospital insurance schemes, and a definite desire on the part of the public to provide better medicine and surgery to more people. These complexities make the dilemma being drawn now almost as great as in the beginning, if not more so. The answer to this problem is evolving apparently in three different directions.

The simplest solution is to abolish full-time departments and institute a chair of surgery that carries with it a token salary and allow the professor independence in so far as his surgical practice and private income are concerned. Although immediately there would be a conflict between a demanding private practice and an academic conscience, it is felt by many that with the right type of man occupying the professorial chair this difficulty could be resolved. There are those who feel that such a scheme would work just as well in this country now as it did in Germany two generations ago. Others feel that such a professorship would once again lag too far behind in the sensitive awareness of those sciences basic to surgery.

Another suggestion that has been made also has an element of simplicity: let the federal government finance full-time medical education. Yet to many this would be not only a misuse of public funds but would carry with it an administrative rigidity and administrative obligations that would defeat the very purpose for which full-time clinical departments were established. The restrictions on academic freedom that so often come with various forms of "statism" are still undesired by many.

Finally, full-time departments of clinical surgery can continue to obtain whatever funds they can from outside benevolent sources and at the same time increase the number of private patients seen in order to increase the income of the department. Such funds could easily be used not only to support

the salary of the professor of surgery but also to make it possible for many younger surgeons interested in a scientific career to stay in academic institutions for a longer period of time. During recent years many good institutions in this country have tended toward this latter solution of the problem. Whether this will be successful or not remains to be seen. This, again, is an experiment and one that is well worth adequate trial. The danger, of course, is one of exploitation of the surgeon by the university, for obviously the patients seen will not be limited to those of scientific interest as Welch had once hoped. This exploitation can be limited, even stringently, by the number of private beds available. Another safeguard will be the fact that if the professor of surgery is forced into spending too much of his time in private surgical care the position at that university will lose its attraction for men of great scientific bent and teaching interests. Perhaps a certain amount of exploitation on the part of the university may be justified, for a great university gives much to its professor of surgery in terms of prestige and renown, and who will deny that the care of a few private patients is an enriching experience for the full-time professor?

The solution to the problem of surgical teaching in our universities probably should not be a stereotyped one applicable equally to all universities. It will be necessary for many experiments to be tried in many different environments. There is little to be gained by giving vent to one's emotions in the solution of these problems, but there is much to be offered in consultation between different universities discussing different methods, their problems, and their possible solutions. The problem will always be a dynamic one and will change with the changes in economic and social conditions in our country.

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